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A COMPARISON OF THE EFFICACY OF CHLORAMPHENICOL (CHLOROMYCETIN) AND OF PENICILLIN IN THE TREATMENT OF PNEUMOCOCCAL LOBAR PNEUMONIA

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Received for publication June 30, 1952

In a previous report (1) reasons for investigating alternative forms of therapy in infections for which suitable remedies are already available were set forth. The present study represents a continuation of the investigation of the efficacy of the several therapeutic agents available for the treatment of pneumococcal lobar pneumonia. Although chloramphenicol has been shown to exhibit antipneumococcal activity both in the laboratory and in the clinic (2, 3, 4, 5), relatively few data concerning its use in the treatment of lobar pneumonia due to pneumococcus have been published. For that reason, the efficacy of chloramphenicol was compared to that of penicillin in the management of this specific infection of the respiratory tract.

METHOD OF STUDY

The study included all patients admitted with the clinical diagnosis of lobar pneumonia to the general medical wards of the Johns Hopkins Hospital and the U. S. Public Health Service Hospital of Baltimore during the period July 1, 1951 to May 31, 1952. The following studies were carried out on admission: X-ray of the chest, leukocyte count, blood culture and a study of the sputum by direct smear, Quellung reaction, culture and mouse inoculation. The assessment of the severity of illness on admission was based upon the objective historical, physical and laboratory findings listed in Table I, together with the clinical impression of the attending physician at the time of his initial examination of the patient.

The patients were divided into two comparable groups, one receiving chloramphenicol[1] orally, the other penicillin by intermittent intramuscular injection. All patients whose history number ended in an odd integer received chloramphenicol (Schedule A) and all whose history number ended in an even integer received penicillin (Schedule B).

Patients on Schedule A received 1 gram of chloramphenicol orally on admission and 1 gram of chloramphenicol every six hours thereafter. Treatment was continued until the rectal temperature was below 99.6°F for 72 hours. Patients on Schedule B received 300,000 units of sodium penicillin G in aqueous solution intramuscularly at the time of admission, at the next 8 o'clock treatment period (A.M. or P.M.) and every 12 hours thereafter, until the rectal temperature was below 99.6°F for 72 hours.

During the course of illness, the following observations were made: rectal temperature every 4 hours; white blood cell count daily until normal, then twice weekly; measurement

[1] The chloramphenicol and penicillin used in this study were supplied by Parke, Davis and Company through the courtesy of Dr. E. A. Sharp

of hematocrit on days 1 and 2, then twice weekly; urinalysis on days 1, 2, and 3, then twice weekly; X-ray of the chest before discharge or as otherwise indicated.

All patients admitted with a clinical diagnosis of lobar pneumonia in the period noted above were included initially in this study. Those in whom the diagnosis could not be substantiated by the isolation of a pneumococcus and by the roentgenographic demonstration of pulmonary consolidation were excluded subsequently. Excluded also were three patients who did not receive chloramphenicol according to the prescribed protocol. One mildly ill patient received penicillin through error and another mildly ill patient who had been treated with penicillin for four days prior to admission was continued on that drug. A third patient, moderately ill, received chloramphenicol and penicillin concomitantly and was therefore not included in the series. All three patients recovered uneventfully.

RESULTS

One hundred two patients were included in the study, forty-three of whom were treated with chloramphenicol (Schedule A) and fifty-nine with penicillin (Schedule B). Judged by the criteria outlined in Table I, the infections were considered to be of comparable severity in the two groups save for the fact that all three critically ill patients were among those treated with chloramphenicol. In the entire series of patients, the severity of the pneumonic processes seemed less severe than in the preceding two years (1, 6), 64.7% of the infections being classified as "mild" in the present study as contrasted with 39.0% and 46.5% of infections listed in this category in the two earlier studies. The diminished severity of illness was reflected also by the low rate of bacteremia which was less than half that found in the years 1949–50 and 1950–51.

Four deaths occurred in this series of patients. Of the three patients treated with chloramphenicol who succumbed, the first was a seventy-seven year old Negro male admitted to the hospital on the seventh day of illness with signs of pneumonia at both lung bases and in severe congestive heart failure secondary to hypertensive cardiovascular disease. Pneumococcus types 13 and 17 were recovered from the sputum; the blood culture was sterile. The nonprotein nitrogen content of the blood was 120 mgm. %. The patient was treated with chloramphenicol in addition to the vigorous measures used to combat his cardiac insufficiency, but his condition remained critical for four days despite the absence of significant fever until the twelve hours preceding death in cardiovascular collapse. Autopsy revealed consolidation of the right middle and lower pulmonary lobes in addition to generalized edema of the lungs and a hypertrophied and dilated heart weighing 570 grams. The second patient was a fifty-nine year old Negro male with severe hypertensive cardiovascular disease who entered the hospital on the first day of a febrile illness which had been preceded by a week's history of symptoms of increasing cardiac decompensation. Examination revealed, in addition to signs of outspoken severe heart failure, consolidation of the lower lobe of the right lung. Type 6 pneumococci were isolated from the sputum but not from the blood. The nonprotein

TABLE I

Analysis of Clinical Data

DATA	PATIENTS GIVEN CHLORAMPHENICOL (Schedule A)		PATIENTS GIVEN I.M. PENICILLIN (Schedule B)		TOTAL	
	No.	%	No.	%	No.	%
Total Patients:	43	100.0	59	100.0	102	100.0
Male	36	83.7	43	72.8	79	77.4
Female	7	16.3	16	27.2	23	22.6
Negro	30	69.8	44	74.6	74	72.6
White	13	30.2	15	25.4	28	27.4
Age of patients:						
Under 40 years	24	55.8	22	37.3	46	45.1
40–59 years	15	34.9	30	50.8	45	44.1
60 years and over	4	9.3	7	11.9	11	10.8
Severity of disease:						
Mild	28	65.2	38	64.4	66	64.7
Moderate	12	27.9	14	23.7	26	25.5
Severe	0	0	7	11.9	7	6.9
Critical	3	6.9	0	0	3	2.9
Duration of illness before therapy:						
1 or 2 days	18	41.9	18	30.5	36	35.3
3 or 4 days	14	32.6	27	45.8	41	40.2
5 or 6 days	8	18.6	10	16.9	18	17.6
Over 6 days	3	6.9	4	6.8	7	6.9
Indications of severity:						
Bacteremia	4	9.3	6	10.2	10	9.8
Multilobar involvement	11	25.6	14	23.7	25	24.5
Leukocytes less than 8,000 per cu. mm.	4	9.3	4	6.8	8	7.8
Shock	1	2.3	0	0	1	1.0
Disorientation	5	11.6	7	11.9	12	11.8
Jaundice	1	2.3	2	3.4	3	2.9
Alcoholism	13	30.2	18	30.5	31	30.4
Other complicating diseases*	11	25.6	18	30.5	29	28.4
Pneumococcal types:						
1–8	31	72.1	47	79.7	78	76.5
Higher types	11	25.6	10	16.9	21	20.6
Untyped	1	2.3	2	3.4	3	2.9
Patients receiving prior treatment	0	0	0	0	0	0

* Cardiac failure, diabetes, liver disease, etc.

nitrogen content of the blood was 135 mgm. %. The patient was treated with chloramphenicol and received also two injections of 300,000 units of penicillin because of his critical state. He died, nevertheless, thirty hours after admission

and autopsy demonstrated in addition to a greatly enlarged and dilated heart weighing 700 grams, consolidation of the middle and lower lobes of the right lung from which a few viable type 6 pneumococci were recovered. The third patient who received chloramphenicol and expired would have been treated with penicillin according to the protocol had he not manifested hypersensitivity to penicillin on previous contact with this drug. He was a fifty-nine year old Negro male with advanced arteriosclerotic heart disease who entered the hospital in heart failure, uremia and shock with signs of pneumonia involving the middle and upper lobes of the right lung and the upper lobe of the left lung. Type 6 pneumococcus was isolated both from the sputum and from the blood. He remained afebrile throughout his three days of hospitalization, but he failed to respond to supportive measures and chloramphenicol and died. An autopsy was not performed. Two patients treated with penicillin expired but the death of one took place over a month following admission and resulted from causes unrelated to the respiratory infection leading to her hospitalization. Because autopsy revealed no evidence of pneumonia, this death is not considered to be the sequel to pneumococcal infection. The remaining patient was an eighty-two year old white female admitted on the third day of illness with lobar pneumonia involving the right lower lobe due to pneumococcus type 7. The leukocyte count was 17,600 per cu. mm. and the blood culture was sterile. The patient was unresponsive on admission and had a temperature of 103°F. She was treated with the prescribed amount of penicillin for three days during which time she continued to have remittant fever and leukocytosis. For this reason, the dose of penicillin was doubled and the patient defervesced gradually. She never became responsive, however, and died quietly nine days after admission. Permission for autopsy was denied.

The protocol for treatment with chloramphenicol was maintained in all patients with the exception noted above. In the series of patients treated with penicillin one individual severely ill with bilateral pneumonia due to pneumococcus type 2 was given terramycin in addition to penicillin after the seventh day of treatment because of persisting fever. Both drugs were continued and the patient became afebrile on the fourteenth day of hospitalization.

Complications occurred in approximately equal numbers in both treatment groups. Resolution of the pneumonic process was delayed beyond three weeks in four patients receiving chloramphenicol and in an equal number treated with penicillin. In three patients of each treatment group, pleural effusion, necessitating thoracentesis in three instances, developed. One patient in each treatment group gave evidence of pulmonary excavation as resolution of the pneumonic process proceeded. All patients with complications recovered.

Toxic manifestations resulting from either form of therapy were infrequent. One patient treated with chloramphenicol developed fever, diarrhea and moderately severe stomatitis on the eighth day of administration of the drug

but no fungi were demonstrated in cultures of the surface of the inflamed mucous membrane. Symptoms subsided promptly on withdrawal of the drug as they did in a second patient who developed nausea, vomiting, and diarrhea on the sixth day of treatment. A third patient manifested leukopenia on the fourteenth day of chloramphenicol therapy, his white blood cell count falling from a high of 9,600 per cu. mm. to 2,900 per cu. mm. without significant alteration in the differential white blood cell count or in the appearance of platelets in the blood smear. A week following discontinuance of the drug, the leukocyte count had risen to 6,040 per cu. mm. One patient treated with penicillin developed dermatitis medicamentosa on the third day of treatment. Administration of penicillin was discontinued and the patient recovered uneventfully without additional therapy. Another patient receiving penicillin manifested a fall in white blood cell count to 3,800 per cu. mm. without untoward effect.

TABLE II

Results of Treatment

DATA	PATIENTS GIVEN CHLORAMPHENICOL (Schedule A)		PATIENTS GIVEN I.M. PENICILLIN (Schedule B)		TOTAL	
	No.	%	No.	%	No.	%
Total Patients	43	100.0	59	100.0	102	100.0
Duration of fever following start of therapy						
1 day or less	15	34.9	17	28.8	32	31.4
2 days	8	18.6	8	13.5	16	15.7
3 days	8	18.6	5	8.5	13	12.7
4 days or more	12	27.9	29	49.2	41	40.2
Duration of WBC greater than 10,000 per cu. mm.*						
3 days or less	12	27.9	26	44.1	38	37.2
4–6 days	18	41.9	16	27.2	34	33.3
7 days or more	5	11.6	12	20.4	17	16.6
Complications	9	20.9	10	16.9	19	18.6
Deaths	3	6.9	1	1.7	4	3.9

* Thirteen patients did not have a white blood cell count as high as 10,000 per cu. mm. during their illness.

DISCUSSION

The data collected in this comparative examination of the efficacy of chloramphenicol and of penicillin in the treatment of pneumococcal lobar pneumonia indicate that both drugs are therapeutically beneficial. The dose of chloramphenicol employed was doubtless in excess of that required to treat un-

complicated pneumococcal infection of average severity, for it has been shown that recovery will ensue in many instances following the administration of one gram daily (4). The somewhat higher death rate in the group treated in this study with chloramphenicol is due in part to the fact that all three patients who received this drug and died had far advanced heart disease and were unable to tolerate the added stress of infection. Of these, one was a critically ill patient who should have received penicillin according to the protocol but was given chloramphenicol because of a history of hypersensitivity to the former drug. Like aureomycin, chloramphenicol provides an alternative form of therapy for those with a history of hypersensitivity to penicillin and it manifests also antibacterial activity against a comparable diversity of bacterial species. This latter fact may make the use of chloramphenicol preferable to that of penicillin at times when facilities for establishing the etiology of an acute pulmonary infection are not available. No serious toxic manifestations resulted in this study from the use of either chloramphenicol or of penicillin and the stimulating effect of the former drug upon gastrointestinal motility was less pronounced than that following the use of aureomycin (1). Both chloramphenicol and aureomycin cause significant changes in intestinal flora (7), however, and administration of either may be followed at times by secondary fungal infections (8, 9). Of greater importance is the more recently reported occasional depressant effect of chloramphenicol upon the bone marrow (10, 11). The fact that fatal thrombocytopenia and aplastic anemia have followed the administration of this drug by others makes its use less desirable in the treatment of infections for which other equally satisfactory and less toxic agents are available. If chloramphenicol is to be employed, it should not be administered without careful inquiry regarding previous contact with the drug and without careful and repeated examination of all formed elements of the blood. Failure to employ these precautionary measures constitutes negligence. Review of the data collected from the literature and of those gathered during the past several years by the hospitals in Baltimore participating in the study of pneumococcal lobar pneumonia indicates that, although chloramphenicol and aureomycin are highly effective in such infections, penicillin is no less effective and is probably less toxic and less costly than either of these alternative forms of treatment.

SUMMARY

In a comparative study of the efficacy of chloramphenicol and of penicillin in the treatment of pneumococcal lobar pneumonia, chloramphenicol was found to be an effective drug in the management of this infection. Because it may give rise to serious toxic reactions, however, chloramphenicol is recommended only as an alternative form of therapy.

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THE ANTIDIURETIC ACTIVITY OF SOME ORGANIC ACIDS[1]

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Marshall and Blanchard (1) found both 3-hydroxyquinaldine-4-carboxylic acid and 3-hydroxy-2-phenylcinchoninic acid to exhibit a pronounced antidiuretic activity upon administration to dogs experiencing a water-induced diuresis. Subsequently, a number of derivatives of these two acids were found to act similarly and the relative antidiuretic potencies of these derivatives were determined (2, 3). In continuation of these previous investigations the relative antidiuretic activities of several new derivatives of cinchoninic acid and of some cognate acids have been determined.

The two members of this class of antidiuretic drugs of greatest potency are 3-hydroxyquinaldine-4,8-dicarboxylic acid and 3-hydroxy-2-phenylquinoline-4,8-dicarboxylic acid (2). These substances upon heating in an inert solvent are converted to, respectively, 3-hydroxyquinaldine-8-carboxylic acid and 3-hydroxy-2-phenylquinoline-8-carboxylic acid. These acids are structural isomers of 3-hydroxyquinaldine-4-carboxylic acid and of 3-hydroxy-2-phenylcinchoninic acid. Unexpectedly both of these new derivatives of quinoline-8-carboxylic acid were found to exhibit antidiuretic activity. Because of this and because the monohydroxy derivatives of cinchophen are structural isomers of 3-hydroxy-2-phenylcinchoninic acid, 7-, 8- and 2′-hydroxycinchophen were assayed for antidiuretic activity. Similar assays of a number of other acids, structurally unrelated to cinchoninic acid and its congeners, have likewise been made. The particular acids chosen for examination were selected in part as a result of speculations of a purely chemical nature and in part as a result of speculations concerning the metabolic fate of 3-hydroxy-2-phenylcinchoninic acid. Only a fraction of the dose of this substance administered to the rabbit, dog or man is excreted in the urine (4). The nature of the end products of this metabolic degradation is presently unknown.

It has been claimed (5, 6), although never substantiated, that one of the end products of the metabolism of quinaldine in the animal body is N-acetylanthranilic acid. This substance should also be formed upon oxidative degradation of 3-hydroxyquinaldine-4-carboxylic acid. Analogous degradation of 3-hydroxy-2-phenylcinchoninic acid, of 3-hydroxyquinaldine-4,8-dicarboxylic

[1] This investigation has been aided by a grant from the U. S. Public Health Service, and by a grant from the Life Insurance Medical Research Fund.

[2] Sharp and Dohme Fellow in Pharmacology and Experimental Therapeutics.

acid and of 3-hydroxy-2-phenylquinoline-4,8-dicarboxylic acid should result in the ultimate formation of, respectively, N-benzoylanthranilic acid, of 2-acetamidoisophthalic acid and of 2-benzamidoisophthalic acid. Because of this, these four acylamino aromatic acids and the two parent amino acids, anthranilic acid and 2-aminoisophthalic acid were assayed for antidiuretic activity.

In a previous investigation (3) 3-hydroxycinchoninic acid was found to exhibit antidiuretic activity. As this acid may be regarded as a derivative of 3-hydroxyisonicotinic acid and as an isostere of 2-hydroxy-1-naphthoic acid, these two acids were also examined during the course of the present investigation. Mention of the other acids examined will be deferred until the discussion of the experimental findings.

SOURCES AND PREPARATION OF COMPOUNDS

We are indebted to the following individuals for gifts of the substances specified: to Dr. Byron Riegel for 4-quinolinol-3-carboxylic acid (II)[2]; to Mr. W. A. Lott of E. R. Squibb and Sons for 3-phenyl- and 5-phenylsalicylic acids; to Dr. W. C. Meuly of E. I. du Pont de Nemours & Co. for 8-carbomethoxy-3-hydroxy-2-phenylcinchoninic acid (XIV), 8-carboxamido-3-hydroxy-2-phenylcinchoninic acid (XV) and 4-carbomethoxy-3-hydroxy-2-phenylquinoline-8-carboxylic acid (XVI); to Dr. E. J. Cragoe, Jr. of Sharp and Dohme, Inc. for 3-hydroxy-2-(p-xenyl)-quinoline-4,8-dicarboxylic acid (XIII), 3-hydroxy-2-(p-methoxyphenyl)-quinoline-4,8-dicarboxylic acid (XII), 3-hydroxy-6-methoxy-2-phenylcinchoninic acid (VI), and 3-hydroxy-6-methoxycinchoninic acid (V); and to Dr. T. P. Carney of Eli Lilly and Co. for 5-aminonicotinic acid.

The synthesis of N-(3-hydroxy-2-phenylcinchoninoyl)-glycine (VIII) and of N-(3-methoxy-2-phenylcinchoninoyl)-glycine (IX) will be described elsewhere (7). Other substances examined during the course of the present investigation were either purchased from commercial sources or synthesized in this laboratory. The synthetic methods employed for the preparation of known compounds of established structure were essentially those described in the literature cited in table 1. In a few instances previously known compounds were obtained by methods which appear to offer some technical advantage over previously published methods of preparation. These methods and those utilized for the preparation of compounds not heretofore known are described below.

2-Ethyl-3-hydroxycinchoninic Acid (IV). Freshly distilled 1-acetoxy-2-butanone (170 gm., 1.31 mole) was added with shaking in successive portions of approximately 10 cc. each to a solution of 183.8 gm. (1.25 mole) of isatin in 1000 cc. of 5 M sodium hydroxide solution contained in a 3-liter flask. The reaction mixture was boiled gently under reflux for 1¼ hours, left overnight at room temperature, diluted with 500 cc. of water and filtered through a bed of celite. The latter was washed with 50 cc. of water. The filtrate was heated to a temperature of approximately 90° and treated during continuous stirring with 320 cc. of hydrochloric acid (sp. g. 1.19) which was added in a thin stream from a separatory funnel. The mixture was left at room temperature for 5 hours and then filtered. The product was washed with four 50 cc. portions of water, suspended in 1500 cc. of hot water and brought into solution by the addition of ammonia water. The resulting solution was stirred with 15 gm.

[2] Roman numerals have been used to identify compounds for which pertinent data have been assembled in Tables I and II.

of decolorizing carbon for 20 minutes and filtered. The filtrate was heated to just below the boiling point, treated with sufficient hydrochloric acid to make it just acid to congo red and left at room temperature overnight. The precipitated product was separated, washed with eight 30 cc. portions of water and dried to constant weight *in vacuo* at 65°. The deep yellow microcrystalline product weighed 247 gm. (91%). It decomposed at 202–203° when inserted in a bath preheated to 199–200°. For analysis a portion was recrystallized from 5 N hydrochloric acid from which it separated as minute yellow needles which decomposed at 207–208° when inserted in a bath preheated to 199–200°. Henze and his collaborators, who obtained this substance by dealkylation of 3-alkoxy-2-ethylcinchoninic acids, report it to melt at 208–209° corr. (8) and 206–207° corr. (9).

Anal. Calc. for $C_{12}H_{11}O_3N$: N, 6.45.
Found: N, 6.50.

3-Hydroxyquinaldine-8-carboxylic Acid (*XVII*). A mixture of 3 gm. of 3-hydroxy-2-methylquinoline-4,8-dicarboxylic acid (2) and 30 cc. of nitrobenzene was gently boiled under reflux for ¾ hour, cooled to room temperature and filtered. The solid was washed with anhydrous ether to remove nitrobenzene, suspended in 60 cc. of water and brought into solution by the dropwise addition of 6 N ammonia water. This solution was treated with decolorizing carbon, filtered and acidified to congo red by the addition of 6 N hydrochloric acid. The precipitated product (2.28 gm.) was collected and dried at 105°. It was recrystallized by dissolving in warm dimethylformamide and subsequently adding sufficient water to evoke a distinct turbidity. Upon standing overnight the product separated as minute colorless prisms. These were collected, washed successively with 0.5 N hydrochloric acid and ethanol, and dried at 105°. When inserted in a block preheated to 320° with the temperature increasing at a rate of 4° per minute, 3-hydroxyquinaldine-8-carboxylic acid became brown at 332–333°, progressively darkened as the temperature rose, and decomposed at 342–343°.

Anal. Calc. for $C_{11}H_9O_3N$: N, 6.89.
Found: N, 6.86.

3-Hydroxy-2-phenylquinoline-8-carboxylic Acid (*XVIII*). A mixture of 5 gm. of 3-hydroxy--2-phenylquinoline-4,8-dicarboxylic acid (2) and 50 cc. of nitrobenzene was boiled under reflux for 1 hour. The nitrobenzene was removed by steam distillation and the residue from the distillation was suspended in 100 cc. of water and brought into solution by addition of ammonia water. The resulting solution was stirred with 0.5 gm. of decolorizing carbon for 15 minutes and filtered. The filtrate upon acidification to congo red with hydrochloric acid deposited a mass of microscopic yellow needles. These were collected, washed with water and dried at 105°. Yield 3.84 gm. (90%). After recrystallization from hot nitrobenzene, in which this substance is moderately soluble, it was obtained as small very pale yellow prisms which melted without evolution of gas at 323–325° when inserted in a block preheated to 305°.

Anal. Calc. for $C_{16}H_{11}O_3N$: N, 5.28.
Found: N, 5.33.

3-Hydroxy-2-phenylquinoline-4,6-dicarboxylic Acid (*X*). This substance was obtained in 68 per cent yield by the condensation of diketoindoline-6-carboxylic acid (10) with phenacyl acetate in the manner used for the preparation of 3-hydroxy-2-phenylcinchoninic acid (1). For analysis a portion of this preparation was purified by dissolving in hot methylcarbitol (20 cc. per gram) and adding water (20 cc.). The buff colored microcrystalline product which separated upon cooling was dried at 105°. When inserted in a block preheated to 250° it became brown at 248–249°, and decomposed at 315–316°.

Anal. Calc. for $C_{17}H_{11}O_5N$: N, 4.53.
Found: N, 4.60.

Methyl N-benzoylanthranilate. This substance, required for the preparation of N-benzoylanthranilic acid by the method described below, was obtained by the dropwise addition of 14.7 gm. of benzoyl chloride to a solution of 15.1 gm. (0.1 mole) of methyl anthranilate in 30 cc. of pyridine. The reaction mixture was left at room temperature overnight, diluted with 150 cc. of water and the precipitated product collected, washed successively with water and two 5 cc. portions of methanol, and dissolved in 45 cc. of boiling ethanol. Upon cooling, this solution deposited 19.4 gm. (76%) of colorless crystals, m.p. 99–100° (11).

N-Benzoylanthranilic Acid. Sodium hydroxide solution (42 cc. of 1 N) was added to a solution of 10.2 gm. (0.04 mole) of methyl N-benzoylanthranilate in 60 cc. of warm ethanol. The mixture was heated in an open flask on a steam bath for ¾ hour, diluted with 800 cc. of hot water and filtered. The warm filtrate was made faintly acid to congo red by addition of 5 N hydrochloric acid. The voluminous precipitate was collected in a Buchner funnel, washed with three 10 cc. portions of water, and without drying dissolved in a minimum volume of boiling ethanol. Sufficient water to cause the development of a distinct turbidity was added and the solution was left overnight at 5°. The colorless crystalline product which separated from the solution weighed 8.96 gm. (93%) after drying in vacuo. It melted at 182°, as reported by Steiger (12). This method of preparation of N-benzoylanthranilic acid affords a pure product after a single recrystallization. This is not the case when this substance is prepared by the conventional Schotten-Baumann procedure (12).

2-Acetamido-1,3-dimethylbenzene. This substance, required for the preparation of 2-acetamidoisophthalic acid, was obtained by adding 63 gm. of 90 per cent acetic anhydride in a thin stream to a continuously stirred solution of 60.5 gm. (0.5 mole) of 2-amino-1,3-dimethylbenzene in a mixture of 100 cc. of glacial acetic acid and 750 cc. of water. After all of the anhydride had been added, the mixture was stirred for a period of 15 minutes, cooled to room temperature and filtered. After washing with water and drying to constant weight at 105°, the colorless product (76.6 gm., 94%) melted at 175.5–176°, in agreement with the melting point previously recorded for this substance (13, 14).

2-Acetamidoisophthalic Acid. This substance was obtained in 91 per cent yield by oxidizing 2-acetamido-1,3-dimethylbenzene with potassium permanganate in essentially the fashion described by Mayer (15) except that an excess of the oxidizing agent was employed and at the expiration of the reaction the excess was destroyed with alcohol. This procedure prevented the formation of 2-acetamido-m-toluic acid and eliminated the necessity for the purification procedure used by Mayer (15). The crude product, recrystallized from boiling water (16 cc. per gm.) melted at 216–217° when inserted in a bath preheated to 200°.

2-Aminoisophthalic Acid. Concentrated hydrochloric acid (40 cc.) was added to a solution of 10 gm. of 2-acetamidoisophthalic acid in 160 cc. of boiling water. The mixture was held at the boiling point until the separation of solid caused severe bumping (10 minutes), and then heated on a steam bath for an additional ½ hour. A saturated aqueous solution of sodium acetate was then added until the mixture was no longer acid to congo red and the mixture was cooled in an ice water bath. The product was separated, washed with water, dried and recrystallized from boiling ethanol from which, upon cooling, it separated as faintly yellow prisms. These decomposed at 319–320° when inserted in a block preheated to 305–306° with the temperature increasing at a rate of 3° per minute. The melting point of this acid has been reported (17) to be above 340°.

2-Benzamido-1,3-dimethylbenzene. A suspension of 24 gm. (0.2 mole) of 2-amino-1,3-dimethylbenzene in 250 cc. of 10 per cent sodium hydroxide solution was benzoylated in conventional fashion with 26 cc. of benzoyl chloride. The crude product, obtained in essentially quantitative yield, was recrystallized from hot ethanol, from which, upon cooling, it separated as a felted mass of fine colorless needles, m.p. 168–169°. Previous investigators have reported this substance to melt at 164° (13) and 168–168.5° (16).

2-Benzamidoisophthalic Acid. Finely powdered 2-benzamido-1,3-dimethylbenzene (11.3 gm., 0.05 mole) was added in successive small portions to a continuously stirred solution of 31 gm. of magnesium sulfate heptahydrate and 16 gm. of potassium permanganate in 550 cc. of water preheated to a temperature of 80°. During the course of this addition the temperature of the reaction mixture was held at approximately 90°. When all of the permanganate had been reduced, an additional 17.6 gm. of this oxidant was added in successive portions of 1 or 2 gm. each. Upon completion of the oxidation the excess of permanganate was destroyed by the addition of a few cubic centimeters of ethanol and the mixture was filtered. The filter cake was washed with one 75 cc. portion and two 50 cc. portions of boiling water. The combined filtrate and washings were cooled to room temperature and treated with 25 cc. of 5 N hydrochloric acid. The precipitated product was separated, washed with water and dried, first at room temperature and then at 100°, (yield, 12.6 gm., 88%). When inserted in a bath preheated to 190°, the crude acid decomposed at 199–200°. Upon recrystallization from aqueous ethanol, 2-benzamidoisophthalic acid was obtained as long silky needles which decomposed at 221–222° when inserted in a bath preheated to 205°. Kruber (17), who obtained this acid in the form of a dihydrate by oxidative degradation of N-benzoyl-7-methyl-2,3-dihydroindol-3-carboxylic acid, records m.p. 217–218°.

Cinchomeronimide. Following the method of Bachman and Barker (18), a suspension of 15 gm. of cinchomeronic acid in 60 cc. of acetic anhydride was boiled under reflux for 30 minutes and the volatile components of the reaction mixture were then removed by distillation in vacuo. Acetamide (15 gm.) was added to the residue and the mixture was heated under reflux in an oil bath maintained at 100° for 3 days. The solid product (12.22 gm., m.p. 231–232°) was separated, washed with ethanol and used for the following preparation without further purification.

3-Aminoisonicotinic Acid. Chlorine generated by the interaction of 8 gm. of potassium permanganate and 50 cc. of hydrochloric acid was absorbed in 240 cc. of 10 per cent sodium hydroxide solution. Cinchomeronimide (16.7 gm.) was added to this solution, in which it dissolved quickly. The resulting solution was heated to 80°, maintained at this temperature for 5 minutes, cooled to room temperature, brought to pH 5 by the addition of glacial acetic acid, and left overnight at a temperature of 5°. The crystalline product (12.26 gm., 79%, m.p. 297–300°) was collected, washed with water, dried and used without further purification for the following preparation.

3-Hydroxyisonicotinic Acid. A solution of 6.73 gm. of 3-aminoisonicotinic acid in 100 cc. of warm 1 M sulfuric acid was rapidly cooled to 5°, which caused the acid sulfate to separate as very small crystals. This suspension was diazotized by the dropwise addition of a solution of the theoretical quantity of sodium nitrite in 30 cc. of water. The clear solution of the diazonium salt thus obtained was warmed to a temperature of approximately 60°, at which point the evolution of nitrogen began. As the rate of gas evolution abated, the temperature of the mixture was raised to 80° and maintained for 10 minutes. During this time crystals of 3-hydroxyisonicotinic acid began to separate. The mixture was treated with 5 cc. of glacial acetic acid, followed by sufficient ammonia water (12 cc.) to bring its pH to 4 to 5, and then heated until all the separated solid had redissolved. Upon cooling, this solution deposited 6.03 gm. (89%) of pale yellow prisms which melted with decomposition at 313°. Other investigators have reported the decomposition point of this substance to be 315° (19) and 312° (20).

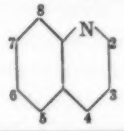
METHODS

The antidiuretic activity of each compound relative to that of 3-hydroxy-2-phenylcinchoninic acid was determined in at least two standardized dogs by the procedure previously described (1, 2). In each instance the rate of the urinary excretion of endogenous creatinine

was determined in order to detect changes in the glomerular filtration rate. This method appeared suitable for our purposes, since Shannon *et al.* (21) have found that in the dog the

TABLE I

Relative Antidiuretic Activity of Acids Derived from Quinoline



Identification Number	POSITION AND NATURE OF SUBSTITUENT GROUPS						Relative Antidiuretic Activity
	2	3	4	6	7	8	
I			COOH				0
II		COOH	OH				0
III(3)		OH	COOH				1
IV(E)	C_2H_5	OH	COOH				½–1
V		OH	COOH	CH_3O			1
VI	C_6H_5	OH	COOH	CH_3O			1
VII(1)	C_6H_5	OH	COOH				1
VIII(7)	C_6H_5	OH	$CONHCH_2COOH$				0
IX(7)	C_6H_5	OCH_3	$CONHCH_2COOH$				0
X(E)	C_6H_5	OH	COOH	COOH			8
XI(2)	C_6H_5	OH	COOH			COOH	160
XII	$p\text{-}CH_3O\cdot C_6H_4$	OH	COOH			COOH	125
XIII	$p\text{-}C_6H_5\cdot C_6H_4$	OH	COOH			COOH	4
XIV	C_6H_5	OH	COOH			$COOCH_3$	5–32
XV	C_6H_5	OH	COOH			$CONH_2$	16–32
XVI	C_6H_5	OH	$COOCH_3$			COOH	40–80
XVII(E)	c CH_3	OH				COOH	½
XVIII(E)	C_6H_5	OH				COOH	4–8
XIX(10)	C_6H_5		COOH			COOH	8–16
XX(22)	C_6H_5					COCH	0
XXI(23)	C_6H_5		COOH		OH		½
XXII(24)	C_6H_5		COOH			OH	¼
XXIII(25)	$o\text{-}HO\cdot C_6H_4$		COOH				¼–½

The numbers in parentheses in the first column of this table indicate the citation in the bibliography in which the preparation of the compound is described. The letter E indicates that the preparation of the compound is described in this communication. The antidiuretic activities of the various compounds relative to that of 3-hydroxy-2-phenylcinchoninic acid chosen as an arbitrary standard are shown in the last column to the right. Compounds which exhibited no antidiuretic activity when administered in a dose four times the minimal effective dose of 3-hydroxy-2-phenylcinchoninic acid have been assigned an activity equal to 0.

clearance of endogenous creatinine affords an approximate measure of the glomerular filtration rate.

DISCUSSION OF RESULTS

The relative antidiuretic activities of the various substances examined in the course of the present investigation are shown in Tables I and II. All of the

acids whose structures are indicated in Table I are derivatives of quinoline, while none of the acids named in Table II are derivatives of this base. With one exception, to be noted later, none of the acids examined had a marked effect upon the rate of excretion of endogenous creatinine. This excretion rate was found to be tolerably constant during the course of a water-induced diuresis and following the administration of non-antidiuretic doses of the antidiuretic acids. In most instances larger doses of these acids did not cause a significant change in the rate of excretion of endogenous creatinine during the period of antidiuretic action. In other instances the drugs caused a transient decrease in this rate of excretion at the beginning of the period of antidiuresis. This effect

TABLE II

Relative Antidiuretic Activity of Miscellaneous Acids

	ACTIVE ACIDS	RELATIVE ACTIVITY		INACTIVE ACIDS
XXIV$_A^*$(E)	N-benzoylanthranilic acid	1	XXVIII	N-acetylanthranilic acid
XXV	N-benzoylisatic acid	¼	XXIX	2-aminoisophthalic acid
XXVI (E)	2-acetamidoisophthalic acid	¼	XXX	5-aminoisonicotinic acid
XXVII	3-phenylsalicylic acid	¼ (?)	XXXI	anthranilic acid
			XXXII	3-benzamidobenzoic acid
			XXXIII	4-benzamidobenzoic acid
			XXXIV	2-benzamidoisophthalic acid
			XXXV	5-bromosalicylic acid
			XXXVI (E)	3-hydroxyisonicotinic acid
			XXXVII	2-hydroxy-1-naphthoic acid
			XXXVIII	2-hydroxy-3-naphthoic acid
			XXXIX	nicotinic acid
			XXXX	3-nitrosalicylic acid
			XXXXI	5-nitrosalicylic acid
			XXXXII	5-phenylsalicylic acid
			XXXXIII	salicylic acid

was comparable in all respects to that of 3-hydroxy-2-phenylcinchoninic acid upon the clearance of exogenous creatinine observed in previous experiments (1).

The results of earlier investigations (1, 2, 3) in this laboratory of the antidiuretic properties of acids derived from quinoline led to the conclusion that in substances of this class, antidiuretic activity is basically determined by the structure inherent in 3-hydroxycinchoninic acid. This conclusion is derived from the observation that the introduction of various substituent groups into positions of the quinoline nucleus, other than those occupied by the hydroxy and carboxy groups of the parent acid, merely alter the antidiuretic action of the parent acid in a quantitative manner provided that the functional integrity of the hydroxy and carboxy groups of the parent 3-hydroxycinchoninic acid is maintained. On this basis one may account for the antidiuretic activities

of compounds I through XVI (Table I). Thus one would not expect either cinchoninic acid (I) or 4-quinolinol-3-carboxylic acid (II), an isomer of 3-hydroxycinchoninic acid (III), to exhibit antidiuretic activity. Similarly, as is the case, one would not expect either N-(3-hydroxy-2-phenylcinchoninoyl)-glycine (VIII) or its methyl derivative (IX) to display antidiuretic activity, because in both of these substances the function of the carboxy group of the parent 3-hydroxy-2-phenylcinchoninic acid (VII) has been destroyed by conjugation with glycine. When the function of the carboxy group in position 4 of the highly potent 3-hydroxy-2-phenylquinoline-4,8-dicarboxylic acid (X) is eliminated by conversion to 4-carbomethoxy-3-hydroxy-2-phenylquinoline-8-carboxylic acid (XVI), one would expect a complete loss of antidiuretic activity. Actually the antidiuretic activity of this ester was found to be one-fourth to one-half that of the parent dicarboxylic acid (XI). One might account for this by assuming that *in vivo* the methyl ester undergoes hydrolysis to the parent acid. However, as will be shown presently, it is possible to account for the activity of the methyl ester (XVI) without postulating the necessity of *in vivo* hydrolysis. Such a postulation is not required to account for the activity of either the isomeric methyl ester, 8-carbomethoxy-3-hydroxy-2-phenylcinchoninic acid (XIV),or the corresponding amide (XV). While these two substances are markedly less potent than the parent dicarboxylic acid (XI), both contain the basic structural features heretofore considered necessary for the exhibition of antidiuretic activity. Accordingly, the decrease in such activity which attends the conversion of the carboxy group in position 8 of 3-hydroxy-2-phenylquinoline-4,8-carboxylic acid to a carbomethoxy or carboxamido group may be regarded simply as an additional example of the effect of a change in the nature of a substituent group upon the antidiuretic activity of the parent 3-hydroxy-2-phenylcinchoninic acid.

A number of acids (Table I, XVII–XXIII) which, although derivatives of quinoline, are not derivatives of 3-hydroxycinchoninic acid, have been found to possess antidiuretic activity. Thus, of these acids, 3-hydroxy-2-methylquinoline-8-carboxylic acid (XVII), 3-hydroxy-2-phenylquinoline-8-carboxylic acid (XVIII) and 2-phenylquinoline-4,8-dicarboxylic acid (XIX) are derivatives of quinoline-8-carboxylic acid. Neither this acid (2) nor its 2-phenyl-derivative (XX) was found to exhibit antidiuretic activity. The latter substance is isomeric with cinchophen (2-phenylcinchoninic acid) which is also devoid of antidiuretic activity. Such activity is however displayed by all four of the isomeric hydroxy derivatives of cinchophen (VII, XXI, XXII, XXIII) so far examined. These facts taken together suggest that in the series of acids under discussion, antidiuretic activity is determined by the presence within the molecule of two acidic groups, one of which may be phenolic, without precise specification as to the position occupied by these groups on the quinoline

nucleus. The hypothesis cited at the beginning of this discussion to account for the inactivity of some derivatives of 3-hydrocinchoninic acid would appear to be a corollary of this suggestion. On this basis the inactivity of 4-quinolinol-3-carboxylic acid (II) and of carbostyril-4-carboxylic acid (I) is probably a consequence of the fact that the hydroxy groups of both 4-quinolinol and of carbostyril fail to exhibit typical phenolic properties, while such properties are characteristic of this group when introduced elsewhere into the quinoline molecule.

While such an hypothesis offers a means of accounting for the main structural features necessary for the exhibition of antidiuretic activity of acids containing the quinoline nucleus, it is of no value in accounting for the activity (or lack of activity) of acids not containing this nucleus. On the basis of this hypothesis one should expect that because of their structural relationship to 3-hydroxy-cinchoninic acid, remarked in the introduction to this paper, both 3-hydroxy-isonicotinic acid and 2-hydroxy-1-naphthoic acid to exhibit antidiuretic properties. Despite this relationship, both of these acids, as well as several other aromatic hydroxy acids (Table II, XXXV, XXXVIII, XXXX to XXXXIII), were found to be devoid of antidiuretic activity under the conditions of our experiments. Only one acid of this class, 3-phenylsalicylic acid (Table II, XXVII), showed antidiuretic activity. This substance, however, unlike the other active acids discussed in this paper, caused a prompt and prolonged decrease in the rate of excretion of endogenous creatinine. In consequence, its relatively weak antidiuretic activity is very probably due, at least in part, to some pharmacological action other than facilitation of the tubular reabsorption of water.

Three acylamino aromatic acids, N-benzoyl anthranilic acid (XXIV), N-benzoylisatic acid (XXV) and 2-acetamidoisophthalic acid (XXVI) exhibit antidiuretic activity. The first two of these were examined because of the possibility that they might be products of the metabolic degradation of 3-hydroxy-2-phenylcinchoninic acid. This is now considered improbable because, following the ingestion of the last named acid (3 gm. in 2 days) by an adult human, we have been unable to detect the presence of N-benzoylanthranilic acid in his urine. Nevertheless, it is a matter of some interest that the antidiuretic activity of this acylamino acid is equal that of 3-hydroxy-2-phenylcinchoninic acid.

The structural features of N-benzoylanthranilic acid and of the other two acylamino acids (XXV and XXVI) found to exhibit antidiuretic activity have little or nothing in common with the acids of the quinoline series. One may, of course, regard the active derivatives of quinoline-8-carboxylic acid as N-substituted anthranilic acids. Similarly, the active derivatives of cinchoninic acid may be regarded as homologs of substituted anthranilic acids. While such a

view affords an apparent chemical correlation between the various acids found to exhibit antidiuretic activity and might be taken to account for the inactivity of acids such as 3-hydroxyisonicotinic acid, this seems of little theoretical or practical import. Indeed, it appears futile to seek any further relationship between the chemical constitution and antidiuretic activity of the various acids. In view of the data now available, it is likely that antidiuretic activity may be a characteristic of a large number of structurally unrelated acids. If this be so, the peculiarities of chemical constitution which distinguish acids having this attribute from those which do not may be a reflection of the manner in which they govern the physiological distribution of the acid, thereby enabling it to reach the locus of action required for the exhibition of antidiuretic activity. Only on this basis can one account for the curious observations, that while neither anthranilic acid nor 2-aminoisophthalic acid are antidiuretic, this property is exhibited by both N-benzoylanthranilic acid and 2-acetamido-isophthalic acid but not by N-acetylanthranilic acid nor by 2-benzamido-isophthalic acid.

As a consequence of this point of view it seems likely that appropriately constituted aliphatic acids may eventually be found to possess antidiuretic activity.

SUMMARY

Forty-three acids of several structural types have been assayed for antidiuretic activity. These assays have shown that such activity is not uniquely an attribute of 3-hydroxycinchoninic acid and its derivatives. Antidiuretic activity is exhibited by certain derivatives of quinoline-8-carboxylic acid and by a few derivatives of anthranilic acid. Because of this, antidiuretic activity does not seem to be determined by any one particular type of chemical structure. Accordingly, it is concluded that the structure of antidiuretic acids is of importance only in so far as it determines the ability of the acid to reach the locus of action.

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FATAL PANCYTOPENIA FOLLOWING THERAPY WITH NUVARONE® (3-METHYL, 5-PHENYLHYDANTOIN). A CASE REPORT*

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The use of Nuvarone in the treatment of epilepsy was the subject of a preliminary report in 1950 (1). No hematologic changes had been observed at that time. It is the purpose of this paper to record a case of fatal pancytopenia which developed in a child who had been receiving Nuvarone therapy. This was the first patient to our knowledge to develop this complication while receiving this drug. However, we have recently been told by a representative of the manufacturer† that one other patient developed aplastic anemia while receiving Nuvarone but recovered after a "long stormy hospital seige" (2).

CASE REPORT

(HLH A-72031)

M. H., a nine year old white girl was seen in consultation in the Private Out Patient Clinic of the Harriet Lane Home in August, 1949. A diagnosis of epilepsy, grand mal was made. Dilantin, 100 mgm., three times a day, and phenobarbital, 32 mgms., three times a day were prescribed and the child returned home to be followed by her family physician.

She was continued on Dilantin and phenobarbital for a period of nine months. At that time because of increasing difficulty in controlling the seizures, and symptoms of Dilantin toxicity, it was decided to replace Dilantin with another hydantoinate, Nuvarone. This was given in a dose of 0.5 gm. three times a day.

The child was examined and blood counts done at approximately monthly intervals. These are recorded in Table I. On September 12, 1951, five months after starting Nuvarone, the child was brought to the family physician's office with the complaint of easy bruising and peculiar mouth lesions of two days duration. Physical examination revealed ecchymotic areas over the arms and legs as well as on the mucous membranes of the mouth although she appeared well and active and was afebrile. Nuvarone was promptly discontinued on the following day when examination of the blood (See Table I, September 13th) revealed pancytopenia. Phenobarbital was continued because of the danger of

* We are indebted to Dr. W. I. Werner of Albuquerque, New Mexico for permission to publish this case and for the information concerning her course and terminal illness.

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TABLE I

Summary of Hematological Determinations Prior to and During Terminal Illness

DATE	GMS. HBG.	MILLION RBC	WBC	% POLYS.	% LYMPHS.	% MONOS.	% EOSINS.	% BASO.	PLATELETS	COMMENTS
8- 8-49	13	4.95	7200	61	38		1		Normal on smear	Initial clinic visit at the Harriet Lane Home
5-11-50	13.5		6300	59	39		2		Normal on smear	Second clinic visit at the Harriet Lane Home
2- 1-51	14.3	5.2	6250	60	34	3	1	2		Subsequent reports through the courtesy of Dr. Werner
4-15-51	14.3	5.6	6350	41	51	3	0	1		Just prior to starting Nuvarone therapy
5-10-51	14.3	5.5	6350	45	51	3	0	1		One month on Nuvarone
6-11-51	16.3	4.5	6250	63	34	3				Two months on Nuvarone
8-29-51	13.5	3.8	4400	44	54	1	1	0		Four months on Nuvarone
9-13-51	10.6	2.7	4300	31	65	2	2		Greatly reduced	Three days after first symptoms of bruising noted, bleeding time was 12 min. 30 sec. and coag. time 13 min. 45 sec.
9-14-51		2.7							None seen	
9-21-51	7.5	2.4	1800	1	99				None seen	Course now progressively downhill with high fever and increasing bleeding tendency
9-22-51			3600	0	98		2			Transfusions given
9-24-51	4.4		2450	0	100					
9-26-51	6.0	2.1	1400	0	100					
9-28-51	9.7	3.6	1050	0	100					Day of Death

precipitating status epilepticus if all anticonvulsant medication was suddenly withdrawn. No history could be obtained of any other drug administration.

On September 17th she was given a fresh whole blood transfusion without incident. She continued to feel well although there was a slight temperature elevation on the following day. On September 19th the temperature rose to 40.3°C. From that day until her death the temperature ranged from 38.4°C. to 40.6°C. Therapy consisted of repeated fresh whole blood transfusions, penicillin, aureomycin, capsules of Rubraferate and general supportive measures. Despite the prompt withdrawal of Nuvarone the pancytopenia become progressively worse, profuse gastrointestinal bleeding developed, and on the 28th day of September, eighteen days after the onset of her symptoms, the child quietly expired.

DISCUSSION

The common causes of pancytopenia are usually listed as infection, leukemia, and drug toxicity or sensitivity (3). It is difficult to avoid incrimination of a drug as the toxic factor in this case. In the five months following discontinuance of Dilantin the child received only phenobarbital and Nuvarone. Since phenobarbital rarely, if ever, causes such hematologic changes, and Nuvarone is chemically related to drugs known to cause aplastic anemia, the latter drug would appear to be the toxic agent in this case.

Of the hydantoinates which have received fairly extensive clinical trial—Dilantin, Mesantoin, Thiantoin and Nuvarone—to our knowledge, only Mesantoin, and possibly Dilantin have previously been reported as causing serious damage to the hematopoietic system (4–8). The possibility that the blood changes resulted from Dilantin, discontinued five months prior to the onset of symptoms, seems remote. Indeed, if Dilantin does cause hematologic changes they must be exceedingly rare.

Mesantoin, on the other hand, has repeatedly been implicated as a cause of pancytopenia (4). Of interest here is the close similarity between the chemical structures of Nuvarone (3-methyl, 5-phenylhydantoin) and Mesantoin (3-methyl 5,5-phenylethylhydantoin).

SUMMARY

A case of fatal pancytopenia occurring in association with Nuvarone (3-methyl, 5-phenylhydantoin) therapy is reported.

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DIFFUSE PULMONARY SARCOIDOSIS: DIFFUSING CAPACITY DURING EXERCISE AND OTHER LUNG FUNCTION STUDIES IN RELATION TO ACTH THERAPY

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INTRODUCTION

One of the many manifestations of sarcoidosis is a diffuse infiltration throughout the lungs, which presents an evenly distributed, finely nodular roentgenographic appearance and is frequently associated with severe dyspnea on exertion. This paper is a report of serial pulmonary function studies on three patients with generalized sarcoidosis in whom diffuse pulmonary infiltration was present. Studies were made before, during, and after treatment with adrenocorticotropic hormone, as a part of an extensive study of the effect of ACTH on generalized sarcoidosis which is being carried out at this hospital under the direction of Drs. A. M. Harvey and Lawrence E. Shulman. The purposes for which this paper was written include not only the evaluation of response to ACTH but also an appraisal of the accuracy of the physiological methods used, an amplification of previous interpretations based on these methods, an explanation of clinical signs and symptoms in terms of specific functional abnormalities, and a discussion of pathological and physiological correlations.

With respect to their functional deficit, these patients were similar to those with diffuse pulmonary fibrosis and "alveolar respiratory insufficiency" described by Baldwin, *et al.* (1), and also to those with "interstitial fibrosis or pneumonitis" described by Donald, *et al.* (10). Austrian et al. have reported a series of patients with "alveolar-capillary block," including two with Boeck's sarcoid, in whom the physiological findings were also similar to those reported herein (2). Our findings differ from those of Coates and Comroe in their series of five patients with diffuse pulmonary sarcoidosis (3), in that there was no evidence of generalized airway obstruction in any of our patients. In their excellent review of the general subject of sarcoidosis, Longcope and Freiman discuss the various forms of diffuse pulmonary sarcoidosis (15).

Two recent papers report the effect of ACTH on the pulmonary function of patients with various forms of chronic pulmonary disease (4, 5). Each series

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includes one case of Boeck's sarcoid. The patient described by Galdston et al. (4) apparently had less severe pulmonary involvement than our patients since, unlike our patients, both the ratio of venous admixture to total blood flow and the diffusing capacity were normal. As in our patients, however, there was a reduction in ventilatory capacity and an increase in the ratio of dead space to tidal air, with subsequent improvement in these measurements on ACTH therapy. All patients in Lukas' series showed obstructive emphysema (5). His one case of pulmonary sarcoidosis was, therefore, not comparable to ours.

As far as the authors are aware, there have been no previous studies in which the diffusing capacity and the distribution of blood and gas in the lungs have been determined during exercise in patients with pulmonary disease. We believe that these values make possible a more precise isolation of specific physiological factors and lead to a more complete explanation of the clinical signs and symptoms. These findings, then, constitute the part of the present

SYMBOLS USED IN TABLES AND CHARTS

BTPS = body temperature and pressure and saturated with water vapor.
B.S.A. = body surface area.
P_B = barometer pressure.
$P_{I_{O_2}}$ = partial pressure of O_2 in inspired gas, in mm. Hg BTPS.
$P^{e}_{A_{O_2}}$ = "effective" alveolar P_{O_2} (9).
Pa_{O_2} = arterial P_{O_2}.
Pa_{CO_2} = arterial P_{CO_2}.
$P_{E_{CO_2}}$ = expired gas P_{CO_2}.
$\dot{V}_E$ = minute volume of expired gas, i.e., ventilation, in 1/min. BTPS.
f = respiratory rate in breaths per minute.
$\frac{\dot{V}_{O_2}}{m^2}$ = O_2 consumption, in ml./min./m.^{2} body surface, STPD.
R = the CO_2–O_2 exchange ratio or respiratory quotient.
V.C. = vital capacity.
M.B.C. = maximal breathing capacity.
V_D^{app} = apparatus dead space to be taken into account with each breath.
V_D^{c} = physiological dead space, corrected for apparatus dead space in ml. BTPS.
$V_D^{c}/V_T^{c} \times 100$ = ratio of dead space to tidal volume, both corrected for apparatus dead space, expressed as per cent (9).
$\dot{Q}va/\dot{Q}t \times 100$ = ratio of venous admixture to total blood flow, expressed as per cent (9).
D_{O_2} = diffusing capacity of the lungs (9).
$S^{e}\bar{c}$ = oxygen saturation of "effective" capillary blood, i.e., blood leaving alveolar capillaries as specifically defined (9).
$S\bar{v}$ = oxygen saturation of mixed venous blood.

TABLE I

Patient C. J.—Effect upon the Calculated Values of $\dot{Q}va/\dot{Q}t$ *and* D_{O_2}/m^3 *Produced by Changes in* $S\bar{c} - S\bar{v}$ *and pH*

REST	$S\bar{c} - S\bar{v}20$	25°	30		pH 7.35	7.40°	7.45	$S\bar{c} - S\bar{v}20$	25°	30		pH 7.35	7.40°	7.45
Date 3/22	$\dot{Q}va/\dot{Q}t$ 17	13	12	$\dot{Q}va/\dot{Q}t$	15	13	12	D_{O_2}/m^3 5.7	5.2	5.2	D_{O_2}/m^3	5.5	5.2	5.0
4/5	10	8	7		8	8	8	5.2	4.6	4.6		4.7	4.6	4.6
EXERCISE	$S\bar{c} - S\bar{v}35$	40°	50		pH 7.35	7.40°	7.45	$S\bar{c} - S\bar{v}35$	40°	50		pH 7.35	7.40°	7.45
Date 4/9	$\dot{Q}va/\dot{Q}t$ 6	5	4	$\dot{Q}va/\dot{Q}t$	5	5	4	D_{O_2}/m^3 16	15	14	D_{O_2}/m^3	15	15	14
4/23	4	3	3		4	3	3	16	14	14		15	14	14
5/4	7	6	5		7	6	5	17	16	15		16	16	15
5/21	17	15	13		16	15	14	11	11	10		11	11	11
5/29	17	15	12		16	15	13	11	11	10		11	11	10
9/11	6	6	5		6	6	5	12	11	11		11	11	11

This table demonstrates the manner in which $\dot{Q}va/\dot{Q}t$ and D_{O_2}/m^3 vary when different values for $S\bar{c}$-$S\bar{v}$ and pH are used in the calculations. In the present studies neither $S\bar{c}$-$S\bar{v}$ nor pH were known. The starred values were used in the calculations shown in the other tables and charts of this paper. This table provides evidence that errors arising from use of the assumed values were probably insignificant.

studies which is new from the physiological point of view, and they will accordingly be discussed in some detail. The application of the new methods to the problem of diffuse pulmonary sarcoidosis and its response to ACTH therapy adds further information of clinical interest and demonstrates both the value and the limitations of these functional studies in elucidating a clinical problem.

METHODS

The patient received no sedation and came to the laboratory in the morning after breakfast.

Respiratory valves and corrugated rubber tubing were arranged so as to conduct the expired gas to a large (500 liter) gasometer with a recording device attached. For resting studies "J" valves and standard one inch tubing were used. For studies during exercise, a special high velocity valve* and special large bore (1½ inch) tubing were used. The apparatus dead space to be taken into account with each breath was carefully measured by water displacement. This included the volume between the respiratory valves plus the volume contained in the mouthpiece. The apparatus dead space occasionally varied because different valve housings were used, and the appropriate values are accordingly listed in Tables III and IV. The entire system was tested for inward and outward leaks at the time of each study.

An indwelling needle was placed in the brachial artery after infiltration with procaine. A noseclip was applied and a mouthpiece adjusted to rest comfortably in the patient's mouth. The collection of expired gas was begun, and during the first 10 minutes the gasometer was flushed repeatedly with the patient's expired gas. A fan inside the gasometer assured complete mixing. The final three minute collection was accurately timed and measured. During the second minute of expired gas sampling, an arterial blood sample was taken in a syringe in which the dead space was eliminated by heparin-fluoride solution† and a drop of mercury. The sampling procedures were the same for resting studies and for studies during exercise. Each study was performed in duplicate, first with the patient breathing room air and then with the patient breathing a low oxygen mixture (usually approximately 14 per cent oxygen in nitrogen).

Exercise was accomplished by walking at a moderate rate on a motor-driven treadmill. The severity of the exercise was further controlled by the angle at which the treadmill was tilted. To facilitate arterial blood sampling, the patient steadied his arm by grasping gently an upright iron pipe.

The blood sample was rotated to insure mixing with the anticoagulant-antiglycolytic solution, and was immediately analysed for P_{CO_2} and P_{O_2} by the bubble equilibration method of Riley, *et al.* (6). The expired gas was mixed for three minutes in the gasometer with the fan turned on. An aliquot was then analysed for CO_2 and O_2 in the Scholander 0.5 ml. gas analyser.

Calculations were performed according to the system of analysis first described by Lilienthal, *et al.* (11) and more recently amplified by Riley, Cournand, and Donald (7) The "effective" alveolar P_{O_2} was calculated from inspired P_{O_2}, arterial P_{CO_2}, and the CO_2-O_2 exchange ratio (respiratory quotient). The alveolar-arterial P_{O_2} gradient was then sub-

* High velocity respiratory valve, Multiform Products Company, 1421 McGee Street, Kansas City 6, Missouri.

† Roughly 20 units of Heparin Sodium and 0.6 mg. of Sodium Fluoride in 1 ml. of blood.

divided into the diffusion component and the venous admixture component, on the basis of findings at high and low levels of oxygenation.

The data obtained during the first study of C. J. on March 22, 1951 (Table IV) will serve to illustrate the gradient analysis. When the patient breathed room air, the alveolar P_{O_2} was 98 mm. Hg and the arterial P_{O_2} 75, giving an alveolar-arterial gradient of 23. When the patient breathed a low oxygen mixture, the alveolar P_{O_2} was 66 and the arterial P_{O_2} 49, giving an alveolar-arterial gradient of 17. When these gradients are subdivided into diffusion and venous admixture components, it is found that the diffusion gradient during air breathing was 2 mm. Hg and during low oxygen breathing 12, while the venous admixture gradient during room air breathing was 21 and during low oxygen breathing 5. At each level of oxygenation, the diffusion and venous admixture gradients together comprise the entire alveolar-arterial gradient ($2 + 21 = 23$ mm. Hg and $12 + 5 = 17$ mm. Hg). Finally, the diffusion gradient at the lower level of oxygenation can be used in calculating the diffusing capacity of the lungs, and the venous admixture gradient at the higher level of oxygenation can be used in calculating the ratio of venous admixture to total blood flow. Details of this system of analysis are described elsewhere (7).

The mixed venous blood, which on theoretical grounds is essential to the analysis, was sampled on only one occasion. For all other studies mixed venous blood values were assumed to be such that the "effective" capillary-mixed venous oxygen difference, in terms of percentage saturation with oxygen, was 25 at rest and 40 during exercise. Sample calculations, performed using other values for "effective" capillary-mixed venous blood oxygen difference, indicate that no important errors were introduced by this assumption (Table I). The ratio of venous admixture to total blood flow and the diffusing capacity are the only values in this report which are affected by using assumed values for mixed venous blood saturation. In Table I, the effects upon these values of an error in the assumed figure of plus or minus 5 per cent saturation in the resting studies and of plus 5 and minus 10 per cent in the exercise studies are shown.

Values for pH have likewise been assumed since no significant error is thereby introduced. The pH values, like those for mixed venous blood saturation, affect only the calculations of venous admixture and diffusing capacity in these studies. Accordingly, in Table I, pH values .05 units above and .05 units below the normal value of 7.40 are used to demonstrate the size of any errors which might arise because of assuming a pH of 7.40 in all cases.

SUBJECTS

Serial studies were performed on three colored females with generalised sarcoidosis. Vital statistics for these patients are shown in Table II.

Case No. 1, L. W., a 47 year old clerk was admitted to the hospital on January 25, 1951, with a history of cough for six months, weakness, and weight loss. During this time there had been the gradual development of nodular lesions on the skin of the nose, neck, left elbow, and left knee, as well as conjunctivitis and increasing dypsnea. On physical examination, the patient was markedly dyspneic and showed evidence of weight loss.

The conjunctivae were injected and there were nodules on both corneae. There was generalised glandular enlargement. Examination of the chest revealed dullness at the right base posteriorly, with harsh breath sounds and fine crackling rales throughout both lungs. Splenomegaly and hepatomegaly were present. X-ray examination of the chest revealed some enlargement of the heart, bilateral hilar lymphadenopathy, an obliterated right costophrenic angle, and a mottled, diffuse infiltrate which extended throughout both lungs (see Figure 1a). Biopsy of one of the skin nodules and one of the lymph nodes revealed

sarcoid. The tuberculin test was negative. Hematological and chemical studies were consistent with the diagnosis of sarcoid.

On February 20, the patient was started on daily doses of 50 mg. of ACTH in 1500 ml. of 5 per cent glucose intravenously for a period of three weeks. Following this, the amount of drug was gradually reduced, as shown on Chart 1, and therapy was discontinued on March 27. There was striking subjective and objective improvement in the patient's signs and symptoms. The skin and eye lesions cleared completely, and there was marked clearing of the chest on physical and X-ray examination (see Figure 1*b*). The patient was discharged from the hospital much improved on April 3, although ophthalmological examination on March 31 had revealed some recurrence of the eye lesions. She was followed in the out-patient department for two weeks during which time there was an acute exacerbation of her ocular signs and symptoms, recurrence of the skin lesions, and X-ray evidence of recurrence of the pulmonary infiltration (see Figure 1*c*). She was, therefore, admitted for further treatment on April 16.

Physical examination at that time revealed considerable injection of the right eye with nodules in each iris, both eyelids, the right nasalabial fold, and the neck. There was generalised glandular enlargement, and fine rales were present at both lung bases at the end of inspiration. On April 19, the patient was started on her second course of ACTH. The dosage schedule and preparation used may be seen on Chart 1. Since the patient had relapsed so quickly after the first course, it was decided to follow the intensive intravenous course of ACTH with maintainance doses over a period of months. Accordingly, on May 15, after approximately three weeks of intravenous therapy, she was started on 40 mg. of long acting ACTH in sesame oil intramuscularly twice a day. During this period, there was low-grade fever with two elevations to 103° and 101°F. It was thought that the patient's fever was due to a reaction to sesame oil since there was no apparent flare-up of the sarcoid lesions. (Note the results of pulmonary studies done at this time and see X-ray, Figure 1*d*). The vehicle for and the dosage of ACTH were accordingly changed. All changes in dosage and vehicle are indicated on Chart 1. The patient did well on this regimen and was discharged from the hospital on June 13 to continue treatment on an out-patient basis. On September 15, ACTH was discontinued, but on November 5 recurrence of the ocular and pulmonary lesions again necessitated treatment.

TABLE II

Vital Statistics

PATIENT	DATE	AGE (YRS.)	HEIGHT (CM.)	WEIGHT (KG.)	B.S.A. (SQ.M.)
L. W.	2/ 8/51	47	143	40	1.26
	9/28/51	47	143	54	1.43
C. J.	3/22/51	36	160	52	1.53
	9/11/51	36	160	53	1.54
M. M.	5/12/51	15	161	41	1.39
	11/21/51	15	161	43	1.41

Case No. 2, C. J., a 37 year old domestic worker, was admitted to the hospital on March 16, 1951. The patient had been followed in the out-patient department for several years.

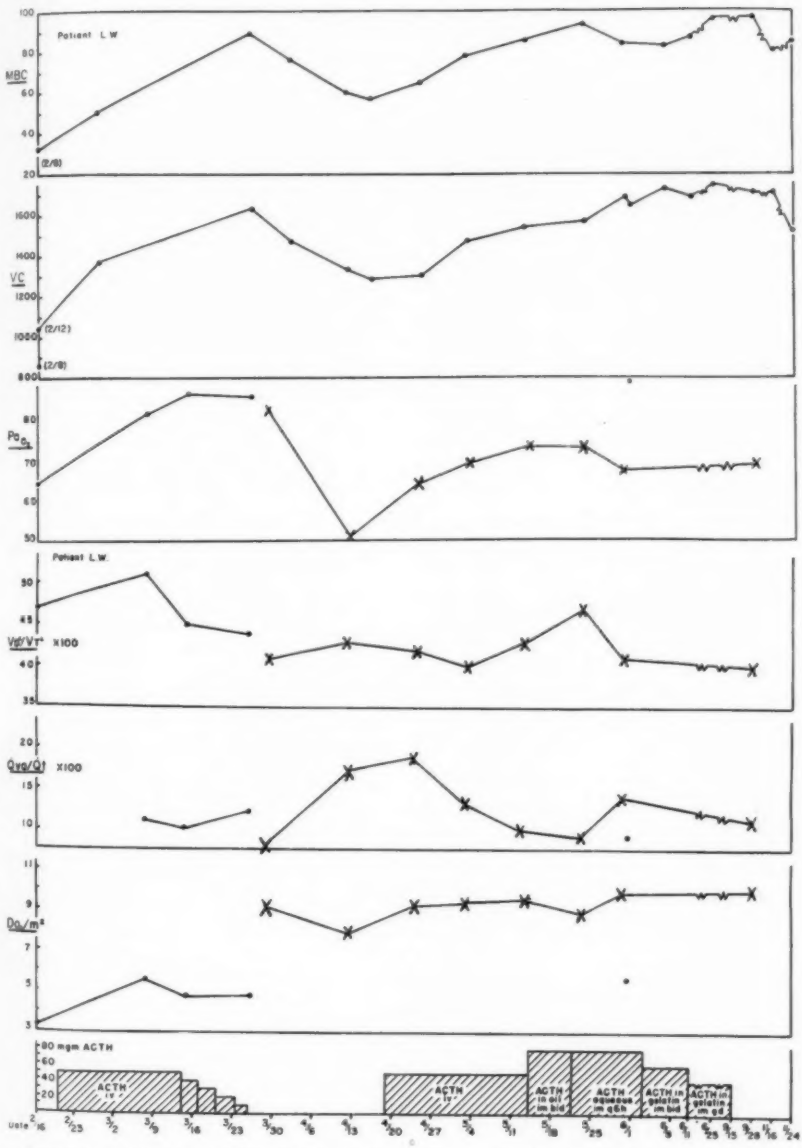

CHART 1. Patient L. W. Ventilation, distribution and diffusion measurements in relation to treatment with ACTH.

○ = at rest
× = during exercise

In 1945, X-ray examination of the chest showed enlarged hilar nodes and a bilateral pulmonary infiltrate. She was sent to a tuberculosis sanitorium for a month. Here many examinations of sputum were found to be negative for acid fast bacilli, and it was found that

FIG. 1*a*

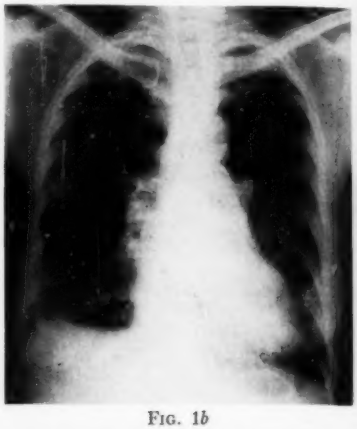

FIG. 1*b*

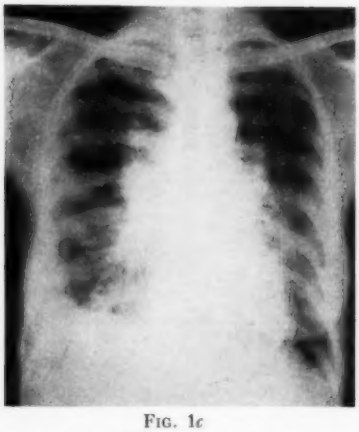

FIG. 1*c*

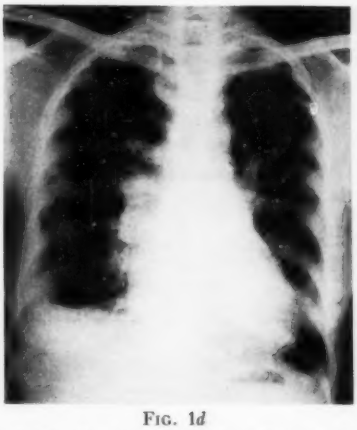

FIG. 1*d*

FIG. 1*a*. Patient L. W. X-ray showing diffuse infiltration in lungs before first course of treatment with ACTH.

FIG. 1*b*. Patient L. W. X-ray showing clearing of pulmonary infiltration at end of first course of ACTH.

FIG. 1*c*. Patient L. W. X-ray showing reappearance of diffuse infiltration in lungs three weeks after termination of first course of ACTH.

FIG. 1*d*. Patient L. W. X-ray showing clearing of pulmonary infiltration approximately two weeks after start of second course of ACTH.

the patient did not react to tuberculin. In 1947, enlarged parotid glands were noted. In January, 1951, the patient had a respiratory infection characterised by fever, sweats, and a productive cough. The cough persisted until the time of admission to the hospital. There was no complaint of dyspnea. In February, a nodule appeared on the left lower leg.

Positive physical findings on admission were placque-like lesions and a nodule on the left lower leg, nodules on the conjunctiva of the left eye and in the iris of the right eye plus retinal lesions, generalised glandular enlargement including the parotid glands, and

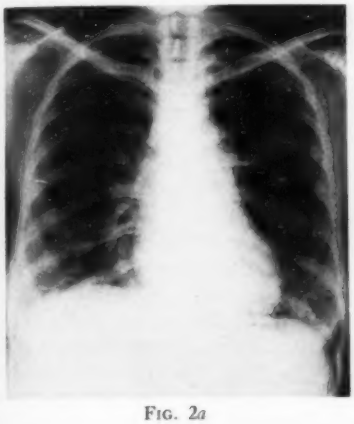

FIG. 2*a*

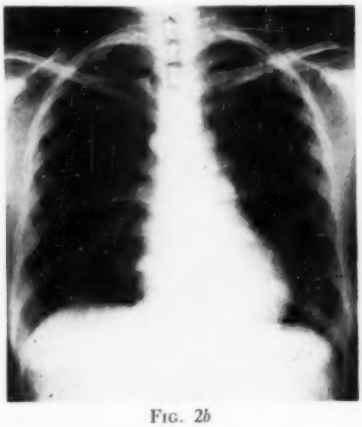

FIG. 2*b*

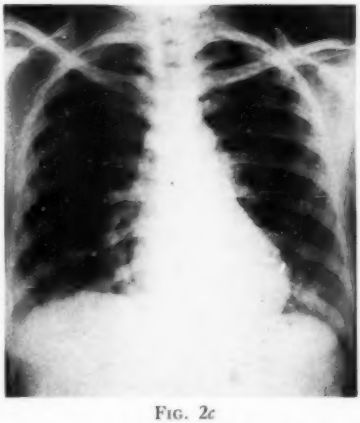

FIG. 2*c*

FIG. 2*a*. Patient C. J. X-ray showing diffuse infiltration of lungs before treatment with ACTH.

FIG. 2*b*. Patient C. J. X-ray showing clearing of pulmonary infiltration after completion of 5 weeks course of ACTH.

FIG. 2*c*. Patient C. J. X-ray showing reappearance of diffuse infiltration in lungs two weeks after termination of course of ACTH.

fine rales at both lung bases heard at the peak of inspiration. The patient had no respiratory distress at rest.

X-ray examination of the chest showed hilar lymph adenopathy and a generalised fine nodular infiltration which was most dense at the lung bases (see Figure 2*a*). Numerous sputa were negative for acid fast bacilli. Biopsy of one of the skin lesions and of a lymph

node showed sarcoid. Hematological and chemical studies were consistent with the diagnosis.

On March 24, the patient was started on a course of ACTH, 50 mg. intravenously in 1000 ml. of 5 per cent glucose per day, for a period of three weeks as shown in Chart 2. Following this, the dose of ACTH was gradually reduced by 10 mg. every third day until April 26 when therapy was discontinued. There was striking clinical improvement with clearing of the skin and eye lesions. The chest became clear to percussion and auscultation and the roentgenogram showed considerable regression of the pulmonary infiltration and hilar adenopathy (see Figure 2*b*).

On April 28, it was noted that the patient again had rales at both bases with other objective signs of relapse, although there were no subjective complaints. A week later she was observed to have a moderate afternoon fever, and the pulmonary signs and symptoms became essentially the same as on admission (see Figure 2*c*). The skin and eye lesions, however, did not reappear. It was decided not to treat the patient again at that time, and she was discharged on May 10 to be followed in the out-patient department.

Case No. 3, M. M., a 15 year old school girl, was first admitted to the hospital in September, 1950, with a history of dyspnea on exertion, fever, and nodular skin lesions on both legs, accompanied by swelling of the knees and ankles. The patient had had rheumatic fever at the age of three. Biopsy of a skin lesion showed sarcoid. She was treated with ACTH, with good results, and discharged in January, 1951.

In May, 1951, nodules appeared on her arms. She noted swelling of her legs and intermittent fever. Dyspnea on exertion reappeared. Shortly after this, iritis developed in the left eye, with subsequent involvement of the right eye. She was readmitted to the hospital on June 8, 1951, for further treatment.

Physical examination at that time showed the ocular lesions described above, nodules on the right and left arms and erythema with slightly tender areas of induration on the legs. The heart was normal and the lungs were clear. There was no splenomegaly or hepatomegaly.

X-ray examination of the chest showed bilateral hilar lymphadenopathy and a reticular infiltrate in both lung fields (see Figure 3). The skin reaction to old tuberculin was positive in a dilution 1:1000. Numerous gastric washings were negative for acid fast bacilli on smear and culture.

On June 29, ACTH, 30 mg. in 1500 ml. of 5 per cent glucose intravenously per day was started and continued for a period of two weeks as shown in Chart 2. The eye and skin signs improved considerably. No improvement could be seen in the chest roentgenogram. Therapy was discontinued owing to a rise in temperature to 103°F. with no other change in signs and symptoms. Following withdrawal of ACTH, the patient's temperature moderated but continued to rise to 100°F. each night. By July 22, the iritis had recurred; she was again started on 12 mg. ACTH per day intravenously. However, the development of an anaphylactic reaction to the ACTH, manifested by periorbital edema and a generalised papular eruption, made it necessary to discontinue therapy. Small test doses of ACTH (see Chart 2) were tried between July 26 and August 4. These doses were followed by temperature fluctuations of such a degree that further attempts at ACTH therapy were abandoned. The patient was discharged on August 18 at which time the eye and skin lesions were somewhat improved. The chest roentgenogram was essentially the same as on admission.

The patient was seen again on November 21, 1951, when pulmonary studies were performed. The status of the ocular and skin lesions appeared to be similar to that seen in May. Fine showers of rales at the end of inspiration were heard at the lung bases. A creak-

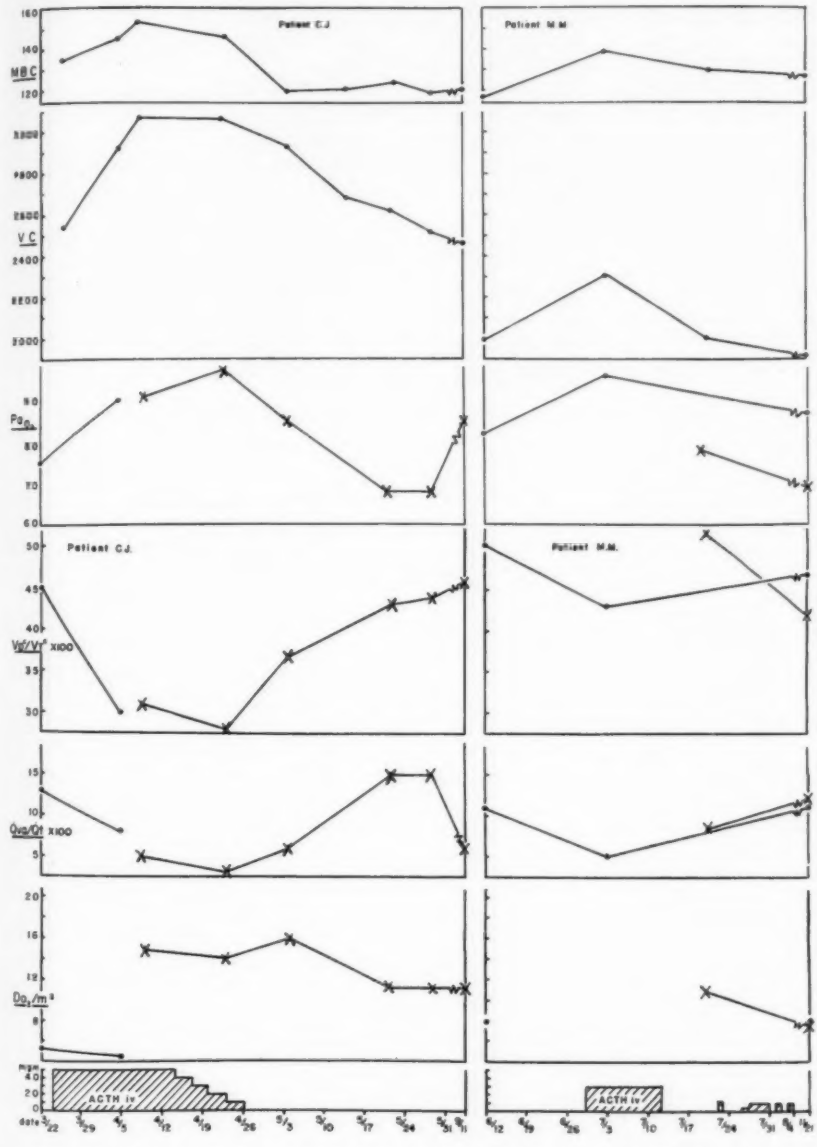

CHART 2. Patients C. J. and M. M. Ventilation, distribution and diffusion measurements in relation to treatment with ACTH.

○ = at rest

× = during exercise

FIG. 3. Patient M. M. X-ray showing diffuse infiltration of lungs before treatment with ACTH.

TABLE III

Gas Exchange Data on L. W.

DATE	ACTIVITY	P_B	$P_{I_{O_2}}$	$P_{A_{O_2}}^c$	Pa_{O_2}	Pa_{CO_2}	$P_{E_{CO_2}}$	$\frac{\dot{V}_E}{m^2}$	f	V_D^{app}	$\dot{V}_{O_2}$	R
2/16/51	Rest	771	150	102	64	41	16.6	7.0	29.3	65	170	.79
			211	169	108	42	15.0	8.3	35.0	65	177	.81
3/ 7/51	Rest	754	148	103	81	42	17.4	6.7	22.7	65	131	.91
			112	73	59	39	16.6	6.4	23.7	65	127	.93
3/15/51	Rest	749	147	108	86	39	15.6	7.4	23.3	110	133	1.00
			107	81	66	32	13.3	9.2	26.9	110	112	1.27
3/26/51	Rest	763	150	111	85	41	16.3	7.1	23.0	110	123	1.09
			101	67	49	37	16.7	7.0	19.9	110	123	1.11
3/29/51	Ex.	758	149	112	82	42	21.8	18.3	31.3	88	452	1.02
			109	76	37	37	19.7	21.5	33.0	88	430	1.14
4/12/51	Ex.	751	147	101	51	41	20.4	17.9	32.0	88	462	.91
			172	122	66	41.5	20.5	17.4	32.8	88	473	.87
4/24/51	Ex.	768	151	109	64	40	20.6	15.6	27.1	88	386	.96
			114	75	40	38	19.6	16.7	30.9	88	388	.97
5/ 3/51	Ex.	752	147	106	69	41	21.4	15.7	29.2	88	391	1.00
			112	73	38	41	20.8	17.1	29.2	88	391	1.06
5/14/51	Ex.	771	151	107	73	44.5	22.2	16.6	28.0	88	413	1.02
			115	76	41	40.5	20.4	18.3	30.7	88	412	1.05
5/22/51	Ex.	753	148	104	73	42	19.9	17.7	31.9	88	417	.95
			108	73	38	37	17.6	20.0	34.8	88	382	1.06
5/29/51	Ex.	749	147	104	67	42	21.8	16.5	28.3	88	420	.97
			108	70	38	40	20.2	18.0	30.7	88	385	1.095
5/31/51	Rest	759	149	112	89	34	16.3	8.8	22.7	110	183	.89
			101	63	39	36	16.7	8.3	23.0	110	168	.95
9/28/51	Ex.	759	149	104	69	42	19.9	14.6	29.0	88	403	.91
			117	76	39	40	20.1	19.0	32.3	88	452	.94

ing sound, similar to a friction rub was heard in mid diastole at the left sternal border in the third interspace. The patient continued to have dyspnea on exertion.

RESULTS

The results of the pulmonary studies, which were carried out at frequent intervals during each patient's stay at the hospital and after discharge to the

TABLE IV

Gas Exchange Data on C. J. and M. M.

DATE	ACTIVITY	P_B	$P_{I_{O_2}}$	$P^{c}_{A_{O_2}}$	$P_{a_{O_2}}$	$P_{a_{CO_2}}$	$P_{E_{CO_2}}$	$\frac{\dot{V}_E}{m^2}$	f	V_D^{app}	$\dot{V}_{O_2}$	R
Patient C. J.												
3/22/51	Rest	757	148	98	75	42	17.3	6.8	22.9	110	168	.81
			100	66	49	37	17.3	6.8	21.3	110	126	1.09
4/ 5/51	Rest	755	148	108	90	40	22.4	6.0	16.7	110	153	1.00
			100	68	53	40	21.4	5.9	18.6	110	114	1.29
4/ 9/51	Ex.	751	147	110	91	39	24.4	20.0	30.5	88	526	1.08
			108	72	54	39	24.0	18.3	29.5	88	469	1.08
4/23/51	Ex.	764	150	110	97	42	27.5	16.3	26.1	88	494	1.05
			110	71	53	42	26.8	16.7	25.6	88	476	1.07
5/ 4/51	Ex.	749	147	106	85	40	22.7	17.8	32.3	88	479	.98
			99	64	43	37	20.2	21.9	35.8	88	488	1.05
5/21/51	Ex.	755	148	111	68	37	19.3	27.7	42.8	88	612	1.00
			108	77	38	34	16.1	29.1	48.9	88	495	1.10
5/29/51	Ex.	749	147	110	68	34	21.8	24.0	28.3	88	512	.91
			111	78	40	32	20.2	26.8	30.7	88	489	.96
9/11/51	Ex.	758	149	107	85	38	19.9	19.9	29.0	88	477	.88
			118	79	52	35	20.1	20.3	32.3	88	457	.87
Patient M. M.												
6/12/51	Rest	760	149	100	82	38	18.0	7.2	17.7	35	199	.74
			113	74	59	32	15.9	8.1	19.3	35	189	.79
7/ 3/51	Rest	760	149	107	96	36	19.5	6.9	16.0	35	190	.82
			84	47*	44*	34	17.3	7.3	19.7	35	159	.92
7/19/51	Ex.	753	148	108	78	34	14.2	19.4	42.8	88	376	.83
			112	74	49	31	12.1	22.2	49.2	88	390	.80
11/21/51	Rest	772	152	114	87	33	17.4	7.7	16.3	35	178	.85
			89	54	35	33	15.9	9.5	15.3	35	180	.94
	Ex.	772	152	119	69	30	14.6	23.6	41.7	88	441	.89
			114	89	38	25	14.0	27.0	41.3	88	442	1.00

* This alveolar-arterial P_{O_2} gradient is too small for accurate analysis and the diffusing capacity has therefore not been calculated from these data. The small gradient is probably the result of technical error.

out-patient department, are tabulated on Table III–VI and plotted on Charts 1 and 2.

The vital capacity before treatment was far below the predicted normal in L. W. and M. M. and moderately reduced in C. J. On the other hand, the maximal breathing capacity, even before treatment, was above normal in the case of C. J. and M. M., indicating excellent mechanical ability to ventilate

TABLE V

Summary of Ventilation, Distribution, and Diffusion Data on L. W.

DATE	ACTIVITY	V.C.	M.B.C.	V_D^c/m^3	$V_D^c/V_T^e \times 100$	$\dot{Q}va/\dot{Q}t \times 100$	D_{O_2}/m^3
			Predicted Normal Values				
	Rest Ex.	2435	62	<100 incr	<30 decr	<6 decr	>10 23
			Actual Values				
2/ 8/51		860	33				
2/12/51		1050	—				
2/16/51	Rest			110	47		3.3
				119	51	—	
2/27/51		1370	50				
3/ 7/51	Rest	—	—	155	51	11	
				127	46		5.5
3/15/51	Rest	—	—	129	45	10	
				141	44		4.7
3/26/51	Rest	1630	89	123	44	12	
				134	40		4.7
3/29/51	Ex.	—	—	265	41	7	
				296	40		9.2
4/ 2/51		1470	76				
4/12/51	Ex.	1330	60	267	43	17	
				259	43		7.8
4/16/51		1280	57				
4/24/51	Ex.	1300	65	263	42	18	
				232	39		9.2
5/ 3/51	Ex.	1467	78	236	40	13	
				277	42		9.3
5/14/51	Ex.	1540	86	286	43	10	
				285	43		9.4
5/22/51	Ex.	1570	94	283	47	9	
				291	46		8.9
5/29/51	Ex.	1690	84	266	41	14	
				278	43		9.9
5/31/51	Rest	1640	—	143	38	9	
				130	38		5.6
6/ 6/51		1730	83				
6/11/51		1690	87				
6/26/51		1750	96				
9/28/51	Ex.	1710	97	254	40	11	
				337	45		10
11/ 6/51		1715	81				
11/24/51		1520	85				

the lungs. In L. W., the maximal breathing capacity was reduced to a half of the predicted normal. She was the only patient of the three who initially showed symptoms of severe respiratory embarassment while at bed rest. In all three patients, the vital capacity and maximal breathing capacity rose

TABLE VI

Summary of Ventilation, Distribution, and Diffusion Data on C. J. and M. M.

DATE	ACTIVITY	V.C.	M.B.C.	$\dot{V}_D$/m²	$\dot{V}_D/\dot{V}_T \times 100$	$\dot{Q}va/\dot{Q}t \times 100$	D_{O_2}/m²
Patient C. J.: Predicted Normal Values							
	Rest Ex.	2905	87	<100 incr	<30 decr	<6 decr	>10 30
Actual Values							
3/22/51	Rest			156	45	13	
				151	40		5.2
3/26/51		2540	135				
4/ 5/51	Rest	2920	145	130	30	8	
				117	31		4.6
4/ 9/51	Ex.	3070	153	287	31	5	
				277	32		15
4/23/51	Ex.	3060	146	243	28	3	
				272	30		14
5/ 4/51	Ex.	2903	120	276	37	6	
				330	39		16
5/14/51		2680	121				
5/21/51	Ex.	2620	124	386	43	15	
				391	48		11
5/29 51	Ex.	2520	119	325	44	15	
				375	47		11
6/ 6/51		2430	117				
9/11/51	Ex.	2460	121	339	46	6	
				331	46		11
Patient M. M.: Predicted Normal Values							
	Rest Ex.	3260	89	<100 incr	<30 decr	<6 decr	>10 40
Actual Values							
6/12/51	Rest	1990	117	261	50	11	
				255	47		7.9
7/ 3/51	Rest	2310	139	240	43	5	
				233	45		*
7/19/51	Ex.	2005	131	277	52	9	
				290	54		11
11/21/51	Rest	1920	127	278	44	11	
				417	50		8
	Ex.			322	45	12	
				318	38		7.5

* Diffusing capacity not reliable because of very small alveolar-arterial P_{O_2} gradient (see Table IV).

with treatment and fell again when ACTH was discontinued. No evidence of obstruction to the inflow of air was seen on the spirographic tracings, and outflow was free except for the last part of the expiratory phase.

Two residual volume determinations were performed on L. W. by Drs. Ross McLean and Richard Shepard. On February 12, 1951 and on March 5, 1951, the values were 960 and 930 ml. respectively. The corresponding total capacity values were 2010 and 2510, and the ratio of residual volume to total capacity changed from 48 to 37 per cent. These values, while suggestive of emphysema, were not associated with any signs or symptoms or airway obstruction, except as noted in the preceding paragraph.

Drs. McLean and Shepard also analysed arterial blood before and after a one minute step test. On February 13, 1951, before ACTH therapy had been started, the arterial oxygen saturation was 83 per cent before and 69 per cent after the exercise. When repeated on March 5, 1951, after two weeks of ACTH therapy, the arterial oxygen saturation was 95 per cent before and 91 per cent after the exercise.

The level of arterial P_{O_2} proved to be a good indicator of the general state of the patient. Directional changes were usually the same as for vital capacity and maximal breathing capacity and bore a definite relationship to ACTH therapy. The arterial P_{CO_2} remained close to the average normal value of 40 mm. Hg in L. W. and C. J. and in M. M., P_{CO_2} decreased progressively. Low values for arterial P_{CO_2} were also observed in patients of this type by Baldwin, *et al.* (1) and by Austrian, *et al.* (2).

Values for the ratio of dead space to tidal volume were consistently higher than normal in each of the patients and tended to fluctuate in the same direction as the ratio of venous admixture to total blood flow in C. J. and M. M. Changes between rest and exercise in the ratio of dead space to tidal volume were not large and were inconsistent, although in normal subjects the ratio decreases on exercise.

In general, the changes in the ratio of venous admixture to total blood flow correlated well with the changes seen clinically in all three patients. The ratio was higher than normal initially, decreased toward normal during treatment, and rose again during relapse. The low final value for C. J. was not consistent with this trend. Exercise values were not very different from those obtained at rest.

The initial diffusing capacity was markedly reduced in L. W. and C. J. The value of 3.3 per m^2, found in L. W., was one of the lowest ever found in this laboratory. Values obtained on exercise were usually higher than those obtained at rest. This difference is always seen in normal individuals and probably indicates that gas exchange takes place across a larger total capillary surface during exercise. In L. W., the values for diffusing capacity obtained during exercise never exceeded the value of 10, which is the lower limit for normal individuals at rest, and improvement in diffusing capacity in response to therapy was not striking. In C. J., the resting diffusing capacity was unchanged after 11 days of treatment. Since no resting value was obtained im-

mediately following treatment for comparison with the initial values, it is not definitely known whether the diffusing capacity improved on therapy. However, since the exercise diffusing capacity decreased after treatment was terminated, it is probable that slight improvement had occurred. In M. M., the diffusing capacity at rest was only slightly low on the two occasions when acceptable determinations were made. These two values were virtually identical to each other. Unfortunately, neither represented the time when maximal improvement had occurred. The exercise value was a little higher one week after ACTH therapy than at the time of the final study several months later, but it was far below normal on both occasions. In none of the three patients did the values for diffusing capacity during exercise show striking improvement in relation to ACTH therapy, and only in C. J. did this value reach as much as one-half of the predicted normal maximal diffusing capacity (Tables V and VI).

Only those results which are to be discussed below have been described above; complete data are presented in the tables and figures.

DISCUSSION

Accuracy of the methods

A precise statement of probable error cannot be given for the values of chief physiological interest since they depend both upon analytic accuracy and upon the patient's willingness and ability to cooperate. For example, certain measurements, such as vital capacity and maximal breathing capacity, require maximal effort on the part of the subject. The accurate determination of certain other values, such as dead space, venous admixture, and diffusing capacity, require that the patient be in a physiologically steady state, whether at rest or during exrecise. This demand is best satisfied when the patient is familiar with the procedures and under no emotional strain. We believe that nearly optimal conditions existed during the studies herein reported as a result of the numerous repetitions of the procedures and the excellent cooperation on the part of the patients.

Analytic errors relate chiefly to the bubble equilibration method for determining blood gas tensions, since the accuracy of the technics for collecting and analysing expired gas is of a much higher order. The bubble method is generally considered to be correct within plus or minus 3 mm. Hg for both P_{CO_2} and P_{O_2}. Since the P_{CO_2} is involved in the calculation of "effective" alveolar P_{O_2}, the total error in the alveolar-arterial P_{O_2} gradient might be 6 mm. Hg when R = 1.0 and even more at lower values of R if individual errors were additive. Variable errors of this magnitude would produce large variations in the calculated values of dead space, venous admixture and diffusing capacity.

There are two chief reasons for our belief that the values actually obtained

did not involve such large errors. The first is the presence of numerous internal checks in the calculations which make errors, if present, apparent. For example, error in P_{CO_2} causes the dead space to vary in one direction and the venous admixture in the opposite direction, yet physiological abnormalities of distribution usually cause these values to vary in the same direction. (In L. W., values for the dead space and venous admixture ratios obtained on May 14 and May 22 are suspect on this account.) Furthermore, the ratio of dead space to tidal volume is usually about the same at high and low levels of oxygenation, yet error in P_{CO_2} determination causes a wide discrepancy. These and other internal checks are, when used with discretion, extremely helpful in detecting errors. The second reason for confidence in the accuracy of the results reported in this paper is the consistency of the values obtained. When the sequence of 12 studies on L. W. is reviewed, it is apparent that gross errors in any one study would stand out from the rest. Each study serves as a partial check on the others.

At the lower level of oxygenation a small technical error in determining the alveolar-arterial gradient leads to a large error in the calculated diffusing capacity if the alveolar-arterial gradient is small; if the gradient is large, a similar small error has much less effect on the diffusing capacity. For this reason it is our policy not to calculate the diffusing capacity if the gradient is less than 6 mm. Hg. The study of M. M. on July 3 is a case in point. Because of the small alveolar-arterial gradient (Table IV), the calculated diffusing capacity comes out very high and is almost certainly in error. This value has accordingly not been recorded in Table VI or in Chart 2.

We conclude that the accuracy of the results herein reported is sufficiently high that the values provide an adequate basis for a preliminary analysis of underlying physiological changes.

Interpretation of results

The vital capacity proved to be a consistent and sensitive guide to the overall progress of the pulmonary manifestations of sarcoid in these patients. There was no trapping of air in the lungs, and the interpretation of the vital capacity could, therefore, be related to structural limitations. X-ray, clinical and physiological findings indicated that the vital capacity was inversely related to the amount of pulmonary infiltration with sarcoid lesions.

The residual volume was not measured in two of our patients. However, constancy of residual volume after ACTH therapy, associated with an increase in vital capacity and total capacity, was found in one of our patients (L. W.) and in another patient with the same type of sarcoid (A. H.) on whom lung volume determinations have been reported in relation to ACTH therapy (8). While maintenance of a constant residual volume following resolution of a

significant mass of sarcoid nodules would seem to require several integrated adjustments, the increase in vital capacity probably results from an increase in distensibility and retractibility of the lung as a whole.

Changes in the maximal breathing capacity closely paralleled those in the vital capacity. While the maximal breathing capacity is a better measure of ventilatory function than the vital capacity, the evidence from the cases reported here suggests that the vital capacity may be equally good or better for quantitating changes in the amount of pulmonary infiltration. The spirograms of these patients showed no evidence of airway obstruction except toward the end of expiration. This helps to explain the well maintained maximal breathing capacities, which were performed in a somewhat inspiratory position and with small tidal volumes but with extraordinary speed.

A standard one minute step test has long been used in the evaluation of pulmonary function and a sharp fall in arterial oxygen saturation after the exercise, such as occurred in the case of L. W., has been recognised as a sign of serious physiological abnormality. When occurring in association with good ventilatory function, a fall in arterial oxygen saturation after exercise has been interpreted as evidence of impaired alveolo-capillary diffusion (1, 2, 10).

Changes in arterial P_{O_2} ran parallel to changes in other indices of the patients condition. This value, however, is the resultant of numerous physiological factors, including ventilation, distribution, diffusion and to a lesser extent circulation, and it must therefore be interpreted in terms of over-all functional integrity rather than specific physiological factors. Since the objective of the system of analysis used in this paper is the isolation of specific factors, we shall emphasize certain derived values which are more helpful than the arterial P_{O_2} from this point of view.

The total dead space reported in these studies represents a volume of gas which is made up of two parts (9). One part might be called true dead space gas and the other dead-space-like gas. True dead space gas includes gas exhaled from the pulmonary airways which are not lined with alveoli and also from groups of alveoli which are not perfused with blood. The dead-space-like gas may be thought of as returning from alveoli which are well ventilated but poorly perfused with blood. More specifically, dead-space-like gas results from variations in the ventilation-perfusion ratio in different parts of the lungs. The increase in dead-space-like contribution is thought to be largely responsible for the abnormally high total dead space figures found in these patients.

The ratio of dead space to tidal volume is necessarily indirectly proportional to the depth of breathing. Both numerator and denominator of the ratio normally increase during exercise, but the tidal volume increases out of proportion to the dead space so that the value of the ratio decreases to well below 30 per cent. In the patients under consideration, the dead space and tidal volume increased almost proportionately during exercise. This is ac-

counted for by the abnormally large increase in dead space and by the abnormally small increase in tidal volume.

Venous admixture, as the term is used here, is made up of two parts comparable to the two components of the total dead space (9). One part can be called true venous admixture and the other venous-admixture-like. True venous admixture consists of poorly saturated blood which enters the oxygenated stream without having picked up any oxygen in the lungs. True venous admixture is typified by the so-called "right to left" shunt. The venous-admixture-like contribution results from variations in the ventilation-perfusion ratio in different parts of the lungs and may be thought of as resulting from the passage of blood through alveoli which are poorly ventilated.

Basically, the distinction between the "true" and "like" effects is one of degree. Both effects result from variations in ventilation-perfusion ratio, but the "true" effects represent the widest possible extremes of such variation. True dead space gas comes from regions with a ventilation-perfusion ratio of infinity, and true venous admixture comes from regions with a ventilation-perfusion ratio of zero. The dead-space-like and venous-admixture-like effects are contributed by regions in which there is an intermediate degree of abnormality in the ventilation-perfusion ratio. Normally the ventilation-perfusion ratio within the alveoli varies only within a narrow range in different parts of the lungs.

Because these patients showed little evidence of airway obstruction, it is tempting to conclude that ventilation was well distributed to alveoli in all parts of the lungs and that variations in ventilation-perfusion ratio must have been due to variations in perfusion of alveoli. The following evidence from the physical examination, however, suggests that there may also have been variations in alveolar ventilation. Two of our patients had showers of very fine rales at the bases, heard only at the peak of inspiration. This finding suggests that some of the very small airways became obstructed by the mass of the sarcoid nodules and that in the inspiratory position, these airways snapped open with the production of tiny rales. If this is the correct interpretation, many of the alveoli at the lung bases were underventilated and, hence, contributed to the over-all abnormality in ventilation-perfusion ratio. We do not believe that this interpretation is incompatible with a normal maximal breathing capacity since, if a considerable proportion of the airways remained unobstructed, the high maximal breathing capacity could have been obtained through these airways without much air passing through the narrowed ones. The high values for maximal breathing capacity obtained after pneumonectomy are consonant with this hypothesis (12).

The diffusing capacity of the lungs is dependent upon the area and permeability per unit area of that part of the total diffusing surface across which gas exchange takes place at the time of the determination. The increase in diffusing

capacity on exercise is believed to arise from an increase in the area of functional capillary bed, resulting from increased cardiac output and increased ventilation, and possibly vasomotor changes. In the present studies, the level of exercise was nearly maximal in all cases, so that the diffusing capacity values obtained during exercise probably approximate maximal values for these patients. The maximal diffusing capacity provides an estimate of the area and character of the total available diffusing surface of the lungs and, therefore, may be conceived of as a structural as well as a functional measurement.* The value for the diffusing capacity at rest is not as easily correlated with the anatomical structure of the lungs because it represents an unknown proportion of the total diffusing surface.

The insignificant change in maximal diffusing capacity in response to ACTH therapy is to be contrasted with the striking diminution in the amount of infiltration which appeared in the roentgenogram of the chest. These findings suggest that the functional damage to the diffusing surface of the lungs was for the most part irreversible and not affected by reduction in the size of the sarcoid nodules, while roentgenographic changes were largely reversible and were related to the size of the nodules. A reasonable explanation for this apparent paradox can be deduced from the pathological changes. When a sarcoid nodule develops it probably destroys the alveolar capillaries which previously occupied the same space. The total diffusing surface of the lungs is thereby reduced and gas exchange is largely diverted to the remaining relatively normal segments of alveolar wall lying between sarcoid nodules. Resolution of the nodule is probably not accompanied by restoration of the destroyed capillaries, so there is little increase in diffusing surface or in diffusing capacity after ACTH therapy. Radiolucency, on the other hand, increases as the nodule shrinks.

The possibility must be considered that in very severe sarcoidosis significant diffusion takes place across the nodules themselves. A discussion of the effects of ACTH therapy upon the diffusing capacity of the lungs as a whole would in this case require consideration of probable changes in resistance to diffusion offered by the nodules. The process of resolution in sarcoidosis, whether spontaneous or induced by ACTH, involves shrinkage of the epithelioid tubercle with deposition of variable amount of collagen. Shrinkage of the tubercle implies reduction in the length of the diffusion pathway. However, resistance to diffusion depends not only upon the length of the diffusion path-

* Further detailed analysis of the theoretical basis of the method for determining diffusing capacity has led to the realization that the diffusing capacity as measured may underestimate the actual diffusing capacity in certain pathological situations. Specifically, an error will be introduced when there is variation in the permeability of the pulmonary membrane for oxygen in different parts of the lung. This error is in such a direction as to exaggerate the discrepancy between normal and diseased persons.

way but also upon the amount of dense collagenous tissue interposed between the alveolar gas and the pulmonary capillary. If a considerable amount of collagen were deposited, the diffusing capacity might show no improvement in spite of radiological evidence of resolution. Thus, regardless of whether gas exchange occurs between nodules, across nodules, or both, there are reasonable explanations for the finding in the cases reported that the diffusing capacity did not increase dramatically after ACTH therapy.

The pulmonary circulation was studied by means of pulmonary artery catheterization on one occasion in one subject (L. W.).* The pulmonary arterial pressure was 42/10 mm. Hg at rest, and 50/7 during exercise. Both of these values are elevated above the normal range. This is the type of pressure response often seen in patients with diffuse pulmonary disease, and indicates increased resistance to the flow of blood through the pulmonary vascular system. It is not known whether the increased resistance occurred primarily in the capillaries or in the small arteries. In the absence of serial measurements of pulmonary artery pressure in these patients, it is not known whether there were pressure changes in relation to therapy. In a single case with comparable clinical and physiological findings, but in whom no etiological diagnosis could be made, West, et al. found a marked decrease toward normal in pulmonary artery pressure following treatment with ACTH (8).

The course of events in this small group of patients, whether followed from the clinical or pathological point of view, shows clearly that the response to ACTH was of short duration. When therapy was discontinued, signs or symptoms of sarcoidosis, particularly the pulmonary component, reappeared within a few days. In the early stages of relapse, the patients were sometimes unaware of any increase in dyspnea on ordinary activity, yet pulmonary changes could be detected early by physiological tests. As far as could be determined, C. J. and M. M. reverted to their original pulmonary status when ACTH was discontinued. In the case of L. W., whose disease was even more extensive than that of the others, ACTH could not be permanently discontinued and maintenance doses have been reinstituted since completion of the present study.

These patients showed other manifestations of sarcoid in addition to those in the lungs, but there was no correlation between the severity of the intrapulmonary and extrapulmonary lesions. In general, both improved on treatment with ACTH and relapsed when treatment was discontinued.

Physiological explanation of clinical signs and symptoms

On clinical and physiological grounds these patients correspond to the group described as having "alveolo-capillary block" (2). This syndrome is charac-

* We are indebted to Dr. Richard J. Bing for this study.

terised by diffuse nodular infiltration throughout both lungs in the chest roentgenogram, dyspnea which becomes extreme on exertion, absence of generalised airway obstruction with high maximal breathing capacity and reduced vital capacity, and cyanosis which is usually not present at rest but which develops during a standard one minute exercise test.

The present studies help to explain the mechanisms underlying the dyspnea and cyanosis of patients with "alveolo-capillary block." It has been demonstrated by Cournand and Richards that the subjective sensation of dyspnea is directly related to the actual ventilation and inversely related to the maximal ventilatory capacity (14). In patients with "alveolo-capillary block," the maximal breathing capacity is not greatly diminished but the actual ventilation in any given state is much increased. The dyspnea can therefore be attributed primarily to the latter factor. The causes of the increased ventilation are two. First, increased total ventilation is necessary in order to maintain normal alveolar ventilation because a relatively large proportion of the total ventilation is ineffective (high ratio of dead space to tidal volume). In the second place, alveolar ventilation itself may in some instances be increased (low arterial P_{CO_2}), causing a further increment in total ventilation. Cyanosis, which occurs in these patients in association with a low arterial oxygen saturation after a standard one minute step test, results in part from the passage of blood through poorly ventilated alveoli (high ratio of venous admixture to total blood flow) and in part from impaired alveolo-capillary diffusion (low diffusing capacity). The latter factor is of particular interest because it does not ordinarily cause significant lowering of the arterial oxygen saturation at rest or during mild steady state exercise. During the more severe exertion involved in a one minute step test, however, a decrease in the arterial oxygen saturation is characteristic. The latter finding is thought to result from a sharp increase in the diffusion gradient for oxygen between the alveolar gas and the blood leaving the alveoli. Theoretical considerations indicate that, when the patient increases his oxygen consumption while breathing room air at sea level, this gradient remains insignificant until a certain work level is reached. As the work load is increased above this level, the diffusion gradient increases rapidly and may become an important factor in relation to decreased arterial oxygen saturation. The level of oxygen consumption at which the diffusion gradient becomes significant depends upon the diffusing capacity of the lungs.

Pathological and physiological correlations

The microscopic alterations in diffuse pulmonary sarcoidosis are less obviously related to the clinical and physiological findings than in certain other diseases which produce "alveolo-capillary block." In the diffuse interstitial fibrosis of Hamman and Rich, for example, the extreme and generalised

thickening of alveolar walls would appear to be compatible with impaired alveolo-capillary diffusion (13). In the milder forms of diffuse pulmonary sarcoidosis scattered epithelioid tubercles are seen but intervening areas appear normal. In more advanced stages the sarcoid nodules become contiguous and occupy a large part of the alveolar space. The lesions do not cause a generalised thickening of the alveolar walls but they lead to a reduction in the number of alveolar capillaries and hence to a reduction in the diffusing surface of the lungs. Furthermore, as discussed above, the diffusion pathway may be lengthened or may lead across dense collagenous tissue. These changes, occurring diffusely throughout all parts of the lungs, interfere seriously with the diffusion characteristics of the lung as a whole. Physiologically they constitute an "alveolo-capillary block."

Microscopic sections also show sarcoid nodules located in relation to small airways and blood vessels. The likelihood of compression of vessels is difficult to estimate, but there can be little doubt that many of the small airways are narrowed. Frequently they appear as narrow clefts between masses of epithelioid tubercles. This appearance suggests that the residual volume should be low unless associated emphysema is present. Furthermore, it suggests that the walls of the terminal airways may frequently be in apposition and that their separation in deep inspiration might produce rales. Finally, the appearance suggests that there might be increased resistance to the flow of air through the narrowed airways. In this case the appearance may be misleading because the microscopic section fails to give any concept of the total cross sectional area of all these small airways when added together. At the level of the higher order alveolar ducts or terminal air sacs the total cross-section is normally so large that no significant resistance to the flow of air is interposed. Approximate calculations indicate that the resistance to flow would remain insignificant even if the diameter of these airways should be reduced to one quarter of the normal.

SUMMARY AND CONCLUSIONS

1. Pulmonary function studies were performed repeatedly on three patients with diffuse pulmonary sarcoidosis before, during, and after treatment with ACTH.

2. Methods for determining the diffusing capacity and for studying the distribution of ventilation and circulation throughout the lungs were applied at rest and during exercise in the steady state.

3. The maximal diffusing capacity was found to be strikingly reduced, indicating impairment of capillary function either by reduction in the number of capillaries taking part in gas exchange or by changes in the characteristics of the diffusing surface. Changes in the maximal diffusing capacity in relation to ACTH therapy were slight.

4. Distribution of ventilation and circulation, as indicated by the ratio of dead space to tidal volume and by the ratio of venous admixture to total blood flow, was seriously impaired. Response to therapy was moderately striking.

5. The vital capacity, maximal breathing capacity, arterial oxygen tension and chest roentgenogram all showed consistent and favorable changes in relation to therapy.

6. In these three cases relapse occurred shortly after cessation of treatment with ACTH.

7. The clinical and physiological findings in these patients were typical of the "alveolo-capillary block" syndrome.

8. The new methods of study which were used help to explain in physiological terms the characteristic signs and symptoms of "alveolo-capillary block."

9. Several correlations between physiological and pathological changes are suggested.

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THE EFFECTS OF ADRENOCORTICOTROPIC HORMONE (ACTH) AND CORTISONE ON SARCOIDOSIS

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In this communication the effect of adrenocorticotropic hormone (ACTH) and cortisone on the clinical course of fifteen patients with sarcoidosis will be described.

The treatment of sarcoidosis has been unsatisfactory in the past. A variety of therapeutic agents have been tried previously, but for the most part any improvement was so slow that it was difficult to know whether it had resulted from the agent given or represented spontaneous recovery. Since the constitutional reaction to sarcoidosis is usually not severe, the most important situation which causes difficulty is the mechanical interference with the function of organs invaded by the disease. Loss of vision, impairment in respiratory function, and death due to failure of the heart or invasion of the kidneys are examples of the difficulties which may ensue in this disease (1). In view of the frequency with which tuberculosis develops in patients with sarcoidosis and because of the possible deleterious effect of intensive adrenal cortical activity on the course of tuberculosis, only those patients have been treated who had serious functional difficulty of the type described above. In addition to an attempt to see whether ACTH and cortisone had any practical therapeutic value in the management of patients with sarcoidosis it was hoped that the degree and nature of the response of the lesions to a high level of adrenal cortical activity might throw some additional light on the nature of the disease process. It was not anticipated that ACTH or cortisone would produce any specific effect on the disease process of a permanent nature. However, just as in the case of disseminated lupus erythematosus where it is known that the disease may enter a spontaneous remission which will last for many years, it was believed that if the active lesions of sarcoidosis could be suppressed by these hormones it might be possible to prevent any serious functional damage during the active phase of the disease and to carry the patients successfully through to a period of spontaneous remission.

Since these studies were begun in 1950, several reports of the use of cortisone and ACTH in patients with sarcoidosis have appeared.

Thorn and his co-workers (2) described the use of ACTH in a case of sarcoidosis with widespread involvement. The patient was given 40 mg. of

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ACTH daily intramuscularly for eight days. It was stated that an adequate adrenal cortical response was obtained. However, no improvement was noted in the clinical state or in the laboratory findings during the short period of treatment. Olson and collaborators (3) observed marked suppression of activity of the uveitis in two patients with probable sarcoidosis who were treated with ACTH. In one case no change was observed in the pulmonary involvement which had been noted on radiological study. Sones and his colleagues (4) reported the results of treatment of two patients with sarcoidosis with cortisone. One received a total of three grams over a period of 15 days and the other 1.8 gms. over nine days. In both patients there was improvement in pulmonary, cutaneous, lacrimal, parotid and lymph node lesions. One patient developed a post-treatment psychosis and was given electroshock therapy. In the second patient, observed several months after the course of treatment, it was stated that the improvement in the lacrimal, parotid and pulmonary lesions was fully maintained. Lovelock and Stone (5) reported short-term observations of two patients treated with cortisone in which there seemed to be definite improvement in the sarcoid lesions while the patients were receiving this hormone. Small (6) reported on the treatment of three patients with cortisone for periods of four to six weeks. Two of the patients had only pulmonary manifestations and one had lymph node and cutaneous involvement as well. There was a rapid regression of the pulmonary and disappearance of the lymph node and cutaneous manifestations. In one case, monthly roentgenograms of the chest were taken for a period of eight months after the start of treatment and the improvement was said to be maintained. The two studies which contain the largest number of cases observed over the longest period of time are those of Michael (7) and Siltzbach (8). Michael has summarized the results of his experience in the administration of cortisone to 10 patients with sarcoidosis. Cortisone was given in a dose of 200 mg. daily for three days followed by 100 mg. daily for one to four months. Patients have been followed for periods ranging from one month up to one year. Symptomatically all patients experienced an increase in their sense of well being which tended to regress upon discontinuation of the hormone. Patients with cough and dyspnea were strikingly improved. In only three instances was it possible to detect objective improvement as measured by an increase in vital capacity. Lymphadenopathy tended to improve slightly during the first 10 days of treatment but no further change was noted. Infiltrative pulmonary lesions showed progressive improvement noted most often toward the end of the second week of treatment and reaching a maximum within six weeks. In no instance were the lungs completely clear even during treatment. Upon cessation of cortisone, lesions showed radiological regression to their initial state. Most dramatic were the changes noted in patients with active iridocyclitis. In only one patient did the ocular inflammation worsen when cortisone was stopped and in this individual cortisone was given in only

60 mg. daily doses for a period of four weeks. Biopsy specimens taken before and during cortisone in two patients revealed no changes which could be attributable to the hormone effect other than some lympholysis. Michael concluded that cortisone does alter the course of sarcoidosis in a favorable fashion. The two most striking features were the clearing of the inflammatory eye lesions and diminution in pulmonary lesions of an infiltrating variety. These lesions required three to four weeks of treatment before showing much improvement and when hormonal administration was stopped the lesions returned to their original level. In no patient did pulmonary tuberculosis develop during cortisone administration. Siltzbach has recently published a complete description of the effects of cortisone in 10 patients with sarcoidosis. Patients were treated for periods ranging from 26 to 106 days. Objective and subjective improvement of varying degree occurred in all patients. It was the impression that fresh lesions appeared to be more responsive than older ones. Of the 10 patients whose course of therapy had been terminated, seven showed a relapse. He summarized the experience to date and found reports of 13 other cases in the literature bringing the combined total of patients with sarcoidosis who have shown objective and subjective improvement of varying degree while under the influence of cortisone to 23. There has been a tendency for the disease to relapse fairly promptly on withdrawal of the drug. This has not been uniformly true however, and maintained improvement might be attributable to the emergence of natural remissions during the period of therapy.

In most of the reported cases cortisone was utilized. In the present study ACTH was utilized almost exclusively. The results are, therefore, of interest for comparison with the reported studies with cortisone.

When intensive treatment with ACTH has been given, the subjective and objective improvement in almost all phases of the disease has been dramatic. The improvement has been maintained throughout the course of administration of this hormone but in most instances within a short period after termination of treatment some degree of relapse has occurred. In three cases, however, no symptomatic relapse has taken place.

Material and Methods

All of these patients were observed for an appropriate time before treatment was begun so that complete clinical and laboratory studies could be made. Of the 15 patients, eight were females and seven males. Ten were colored and five white. The patients ranged in age from 14 to 58 years with an average age of 33. It is extremely difficult to estimate the duration of illness in patients with sarcoidosis. From all the evidence available, the average duration of the disease in these patients was two years with a range of four weeks to six years.

Although in almost every instance the diagnosis could be made satisfactorily from the history and the physical examination, additional evidence was ob-

tained in each case. A biopsy was obtained in 14 patients and the typical microscopic picture of sarcoidosis was present in each instance. The sites of the biopsies were lymph node alone in five; skin and lymph node in six; skin, lymph node and muscle in one; lymph node and liver in one, and orbital mass in one. Twelve patients were studied for rarefaction in the bones by x-ray, and lesions were found in three. Roentgenograms of the chest showed lesions compatible with sarcoidosis in 12 of the 15 patients. There was involvement of the mediastinal nodes and lung parenchyma in nine, the lung parenchyma alone in one and the nodes alone in two. Tests with old tuberculin were done in all patients and were negative to 0.1 mg. in five patients; to 1.0 mg. in nine patients; and to 10 mg. in one.

During the earlier phases of these studies the supply of ACTH was limited. Short courses were given intramuscularly in aqueous solution with a maximum daily dose of 100 mg.; the course of treatment extending over seven to 18 days. In order to produce maximum adreno-cortical stimulation as rapidly as possible most of the treatment given during the past two years has been with ACTH administered intravenously. These 15 patients have received 27 courses of ACTH (Armour) or cortisone (Merck). ACTH has been given intravenously in 17 courses to 12 patients and in an additional three courses has been followed by the administration of Acthar-gel (Armour). ACTH was administered intramuscularly in seven courses to six patients. Cortisone was given by mouth in two courses to two patients and cortisone intramuscularly in one course to one patient. The courses of intravenous ACTH varied in duration from 12 to 42 days with a total dose ranging from 390 to 1650 mg. Intramuscular ACTH was administered from seven to 18 days with the total dose from 360 to 1400 mg. The long-acting material in gelatin was given to three patients over 36 to 130 days in gradually tapering doses from 100 to 20 mg. per day. Cortisone was given by mouth in doses of 200 mg. a day for three to four weeks with gradual reduction toward the end of treatment, and in one patient intramuscularly 100 mg. daily for 14 days.

Depending on the intensity and duration of the treatment, sodium intake was appropriately restricted and a potassium supplement was given daily to each patient treated. Careful clinical and laboratory observations were made to detect any untoward effects from treatment. In Table I the major lesions of sarcoidosis seen in these patients are listed as well as the courses of treatment given and the progress of the disease during and after therapy.

Results

As has been clearly pointed out, the lesions of sarcoidosis fluctuate in their activity. These remissions are quite unpredictable and the activity of the disease may progress in one area while it is declining in another (1). These spontaneous variations usually take place, as far as their objective recognition

is concerned, over periods of months rather than weeks. For this reason an attempt was made, particularly after the very early stages of this study, to give intensive treatment at the onset so that any resulting improvement would be as rapid and as complete as possible and thus clearly attributable to the effect of heightened adrenal cortical activity.

In all patients receiving adequate treatment the response was dramatic. Easily detectable subjective and objective evidence of improvement in the lesions being studied appeared within a relatively short period of time (Table I). The material can, perhaps, be shown best by presenting first a detailed description of one patient with severe sarcoidosis involving the skin, eyes, lungs and liver to a very extensive degree; then the results in the other patients will be briefly summarized; finally a more detailed description will be given of the effect of therapy on the active lesions in various tissues as well as on certain functional abnormalities detectable by laboratory study.

(Case 1, Table I)

This patient (JHH 526041), a 47-year old colored female, entered the hospital on Jan. 25, 1951, complaining of cough, loss of strength and weight, and night sweats for a period of six months. She had also noted skin lesions and difficulty with her eyes for a similar period of time. Her general health had always been excellent in the past. She was said to have had pneumonitis with pleurisy at age 32. There was cessation of menses in May, 1950.

In July, 1950 there was gradual onset of weakness and easy fatigability. She developed a non-productive cough. In the fall of 1950 she began to have frequent night sweats. She also developed "pink eye" and noted appearance of skin lesions on the right side of the nose, the neck, the left elbow and the left knee. As a result of x-ray examinations she was told that she had sarcoidosis. During the next several months she developed edema of the ankles in the evening and noted gradually increasing exertional dyspnea. Up to the time of admssion she had lost about 20 pounds in weight.

Physical examination on admission: T. 103°, P. 120, R. 24, B.P. 110/70. Patient was a very intelligent woman who was tachypneic even at rest and became quite dyspneic on the slightest exertion. She was rather thin and showed evidence of recent weight loss. Small nodular and plaque-like lesions of the skin were seen over the inner canthi, along the right nasal fold, over the left olecranon process, on the nape of the neck and on the left knee (Fig. 1*A*). The conjunctivae were markedly injected. There were mutton-fat deposits on the posterior surface of both corneae. The aqueous ray was strikingly positive. Vision was considerably impaired particularly on the left. The left fundus was difficult to visualize because of cloudiness of the media. On that side vitreous bodies were seen in the inferior part of the fundus. The parotid glands were moderately enlarged having a firm, nodular consistency. There was generalized lymph node enlargement. Chest expansion was greatly limited. There was dulness to percussion at the base of the right lung. The breath sounds were harsh everywhere with prolonged expiration. Coarse and crackling rales were heard in the left mid-lung field anteriorly which were persistent after cough. There was a tachycardia present. The first cardiac sound over the mitral area was accentuated as was the second pulmonic sound. The liver was felt two fingerbreadths below the costal margin in the midclavicular line and the spleen was readily palpable three fingerbreadths below the costal margin.

A variety of laboratory examinations were done. The blood STS was negative. Hematological studies revealed hematocrit 47.5%. Sedimentation rate was 21 mm. per hour.

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Cases of Sarcoidosis Tr *ith ACTH a*

PATIENT, NO., AGE, SEX, RACE	COURSE OF TREATMENT	DURATION OF DISEASE	MANIFESTATION OF DISEASE								Date begun	Horm
			Skin	Eyes	Lymph Nodes		Lungs	Liver	Spleen	Other		
					Peripheral	Mediastinal						
(1) L. W., 562041, 47, F, C	(1)	9 mos.	+++	+++	++	++++	++++	+++	+++	Parotids ++	Jan. 20, 1951	A
	(2)		+	++	+	++++	++	++	+	Parotida +	Apr. 19, 1951	A A se oil A A ge
	(3)		+	+++	+	+++	++	++	+	Parotids –	Nov. 27, 1951	A A ge
(2) B. S., 367372, 28, F, C		6 yrs.	++	++	++	++++	+++	+	+++		Apr. 13, 1951	A
(3) J. C., 524037, 33, M, C	(1)	6 mos.	+++	++	++	++	+++	–	–	Hypercalcemia ++; rena sufficiency +++	Feb. 15, 1950	A
	(2)		+++	–	+	+	++	+	–	Hypercalcemia ++; rena sufficiency +++	Oct. 31, 1950	(
	(3)		+++	+++	+	+	+	++	–	Normal serum calcium; rena sufficiency +++	May 15, 1951	
	(4)		+++	+++	–	+	++	+	–	Hypercalcemia (+) rena sufficiency +; NPN in for 1st time	Mar. 23, 1952	
(4) C. J., 173864, 36, F, C		6 yrs.	+++	++	++	+++	+++	+	+	Parotids ++	Mar. 24, 1951	

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idosis Tr
ith ACTH and Cortisone

TREATMENT						RESULTS DURING TREATMENT	FOLLOW-UP
Date begun	Hormone	Route	Initial dose mgm. or units	Duration days	Total dose mgm. or units		
Jan. 20, 1951	A	i.v.	50	35	1460	Disappearance of dyspnea, rales, uveitis, skin lesions, lymph nodes, hepatosplenomegaly within 2 weeks	Partial recurrence beginning one week after ACTH: sufficiently severe 3 weeks to warrant readmission
Apr. 19, 1951	A	i.v.	50	26	1300	Changes as prompt as during first course	
	A sesame oil	i.m.	80	8	640	Intense inflammation at injection sites with acute exacerbation of activity of disease	
	A	i.m.	80	11	880	Prompt suppression of acute exacerbation	
	A gelatin	i.m.	80	4 mos.		Disease entirely inactive throughout. Asymptomatic and at work	Quiescent for 7 weeks. Then acute severe reactivation of uveitis and slight recurrence of skin, lungs and liver
Nov. 27, 1951	A	i.v.	25	20	440	Prompt clearing of uveitis, skin, nodes and spleen changes. Chest signs and hepatomegaly responded more slowly	
	A gelatin	i.m.	80	3 mos.		Disease entirely inactive throughout. Asymptomatic at work	Asymptomatic and at work for past 3 mos. except for reactivation of uveitis which cleared after 2 wks. with cortisone ointment
Apr. 13, 1951	A	i.v.	50	39	1650	Prompt regression of respiratory symptoms and signs, skin lesions, lymph nodes and hepatosplenomegaly	At 6 wks. entirely asymptomatic without dyspnea. Quiescent but for slight return of eyelid lesions
Feb. 15, 1950	A	i.m.	100	7	550	Rapid disappearance of respiratory symptoms. Fall in calcium to normal. Suggestive improvement in renal function	Transient dyspnea at 1 mo., but at work as laborer for next 8 mos. Moderate hypercalcemia at 1 mo. and renal function at pretreatment state at 2 mos. Return of dyspnea at 8 mos.
Oct. 31, 1950	C	i.m.	100	14	1400	Respiratory symptoms and hypercalcemia regressed slower. No change in renal findings	Returned to work for 6 mos. Asymptomatic until 12 days before admission when severe uveitis and mild cough appeared
May 15, 1951	A	i.m.	100	7	700	Prompt response of eyes, lungs, skin and liver findings. Glaucoma relieved later. Renal function suggestively improved	Asymptomatic for 9 mos. Skin lesions returned at 7 mos. Acute flare-up of uveitis and dyspnea at 9 mos.
Mar. 23, 1952	A	i.v.	5-30	30	650	Beef ACTH hypersensitivity during 1st infusion. No allergic reaction to sheep ACTH. Uveitis became inactive. Calcium to normal. Questionable improvement in renal function	Has not returned since discharge (4/25/52)
Mar. 24, 1951	A	i.v.	50	33	1350	Prompt regression of lung, skin, eye, spleen and parotid involvement	At work for 12 mos. although pulmonary studies indicate relapse, patient remains improved symptomatically. Skin, eyes, lymph nodes, parotids, spleen have remained quiescent

TABLE I—*Continued*

PATIENT, NO., AGE, SEX, RACE	COURSE OF TREATMENT	DURATION OF DISEASE	MANIFESTATIONS OF DISEASE								Date begun	Hormone
			Skin	Eyes	Lymph Nodes: Peripheral	Lymph Nodes: Mediastinal	Lungs	Liver	Spleen	Other		
(5) J. E., 494297, 37, M, W		3 yrs.	++	++	++	+++	+++	−	+	Hypercalcemia ++++; renal insufficiency	Jan. 18, 1951	A
(6) A. H., 561847, 20, M, C		6 mos.	++++	++	++	++++	++++	++	+		Oct. 7, 1951	A
(7) E. M., 568909, 30, M, W		2 yrs.	−	−	+	++++	+++	?	−	Chronic rheumatic heart dis.	May 10, 1951	A
(8) L. D., 453607, 57, F, W		4 yrs.	−	+++	+	−	−	−	−		June 29, 1951	A
(9) J. M., 560400, 58, M, W		2 yrs.	+++	+++	++	−	−	−	−		Oct. 4, 1951	A
(10) L. A., 560330, 16, M, C		16 mos.	−	++++	+	+++	−	−	−		July 16, 1951	A
(11) M. J., 594095, 46, F, C		4 wks.	−	++	−	+++	−	−	−		Jan. 9, 1952	C
(12) B. C., 587942, 18, F, C		5 mos.	+	−	++	++	+	++++	+++	Severe epigastric pain and tenderness; alkaline phosphatase 46 units	Nov. 6, 1951	A
(13) I. N., 596034, 24, F, C		2½ yrs.	+++	++++	++	++	++	++++	++++	Severe muscle involvement; alkaline phosphatase 31 units	Feb. 17, 1952	A
(14) M. M., 105508, 14, F, C	(1)	2 mos.	++++	++	−	+++	+	−	−	Erythema nodosum with edema & severe pain in feet	Oct. 31, 1950	
	(2)		++	+++	+	++++	+++	−	+		June 23, 1951	
(15) R. N., 481401, 38, M, W		3 yrs.	−	−	−	−	−	−	−	Hypercalcemia +; renal insufficiency; right hemiparesis	Nov. 8, 1951	

TABLE I—*Continued*

TREATMENT						RESULTS DURING TREATMENT	FOLLOW-UP
Date begun	Hormone	Route	Initial dose mgm. or units	Duration days	Total dose mgm. or units		
++++; n... Jan. 18, 1951	A	i.m.	100	11	700	Rapid disappearance dyspnea, vomiting; fall of calcium to normal. Skin lesions, lymphadenopathy and splenomegaly disappeared	Asymptomatic at work 1½ yrs. 60 pound weight gain. No vomiting or recurrence of skin lesions
...r. 7, 1951	A	i.v.	50	42	1550	Prompt improvement in respiratory symptoms and signs, skin, eyes, lymph nodes, liver and spleen. Pleural effusion cleared	Asymptomatic at labor for 1 yr. No recurrence of skin, eye, liver, spleen or lymph node involvement. (Vital capacity normal)
...atic heart di... May 10, 1951	A	i.v.	50	28	1200	Prompt improvement in pulmonary symptoms, signs and function	Immediate transient febrile episode. Pulmonary recurrence began at 2 wks.
...June 29, 1951	A	i.v.	30	21	540	Complete clearing of uveitis and retinitis with restored vision with in 2 wks.	Recurrent uveitis and increasing respiratory impairment at 2 mos.
...r. 4, 1951	A	i.v.	50	17	750	Inactivation of uveitis with restored vision and clearing of skin lesions in 2½ wks.	Next 8 mos. on cortisone ophthalmic ointment uveitis completely quiescent, but episcleritis seen for 8 mos.
...July 16, 1951	A	i.v.	40–60	37	1910	Resistant to high doses beef ACTH, moderate response on pork ACTH with inactivation of uveitis; no visual improvement	Transient relapse in uveitis at 1 mo. and again at 7 mos.
...n. 9, 1952	C	p.o.	200	23	3125	Orbital mass regressed to half original size in 2 wks. No improvement thereafter	Unchanged during next 6 wks.
...c pain and h... Nov. 6, 1951	A	i.v.	40	23	700	Prompt relief of abdominal symptoms and regression of hepatosplenomegaly. Phosphatate activity fell to 16.4 units	Early flare up of abdominal manifestations. At 10 wks. asymptomatic without abdominal symptoms. hepatosplenomegaly or fever but phosphatase remained elevated
...nvolvement; ...Feb. 17, ...atase 31 u... 1952	A	i.v.	25	28	100	Inactivation of uveitis, but vision unimproved; fall of phosphatase to 7.3 units. Hepatosplenomegaly, lungs and muscular weakness improved slowly	Partial relapse at 2 wks; at 10 wks. uveitis quiescent, hepatosplenomegaly absent; muscle improvement maintained. Phosphatase 19 units
...um with e... ...t. 31, 1950	A	i.m.	100	18	1400	Rapid regression of erythema nodosum and uveitis. Pain and immobility of feet gone in 36 hours	Progressive pulmonary involvement started at 6 wks. with ocular symptoms and recurrence of nodules
...in feet ...June 23, 1951	A	i.v.	30	13	390	Clearing of uveitis and regression of nodules. Improvement in pulmonary function. Treatment interrupted: sensitivity to beef ACTH	Recurrent uveitis and increasing respiratory impairment at 2 mos.
...+; renal in... ...Nov. 8, ...hemiparesi... 1951	A	i.m.	100	9	720	Serum calcium normal after 6 days. Treatment stopped because of mental deterioration	Died 10 days later at home. Postmortem examination revealed extensive sarcoidosis

Total white count was 4,000 with 60% polymorphonuclear cells, 24% monocytes, and 10% lymphocytes. Urine and stool examinations were normal. Blood chemical examinations revealed: NPN 24 mg. %, fasting blood sugar 68 mg. %, CO_2 25.8 mEq./l. and chlorides 110 mEq./l. Total protein was 6.5 gms. % with 3.4 gms. albumin and 3.1 gms. globulin. Serum calcium was 10 mg. %, serum phosphorus 3.7 mg. %, alkaline phosphatase 3.1 Bodansky units. Cephalin flocculation was 1+, thymol turbidity 10 units, total bilirubin 1.1 mg. % and bromsulfalein retention 20% in 30 minutes. Skin test with old tuberculin (1.0 mg.) was negative. Venous pressure was 145 mm. of water and circulation time 16 seconds with decholin. Vital capacity was 900 cc. and maximal breathing capacity 27 liters. Oxygen diffusion capacity was only 4. These respiratory studies are reported in detail by R. L. Riley, et al. (17). Electrocardiogram revealed no abnormalities other than a sinus tachycardia.

FIG. 1. Patient (1) L. W. Sarcoidosis, treatment with ACTH.

A. Before treatment. Note the plaque-like lesions at both inner canthi and right nasolabial fold.

B. 22nd day of treatment with ACTH. The lesions are no longer visible.

X-ray of the chest revealed some enlargement of the heart. There were bilateral hilar masses and a finely mottled, diffuse infiltration involving almost the entire portion of both lung fields. On the right the costophrenic angle was obliterated by what was interpreted as either fluid or thickened pleura (Fig. 2*A*). Five sputum specimens and three gastric washings were negative for acid-fast bacilli.

A biopsy was taken of one of the plaque-like cutaneous lesions which revealed clusters of epitheloid tubercles typical of sarcoidosis (Fig. 3*A*).

Beginning on February 20 and extending to March 14 the patient received 50 mg. of ACTH intravenously each day by continuous drip lasting over a period of 12 hours. Between March 14 and March 26, the dosage of ACTH was gradually reduced and finally discontinued on the last date (see Chart I). The subjective and objective improvement in this patient's

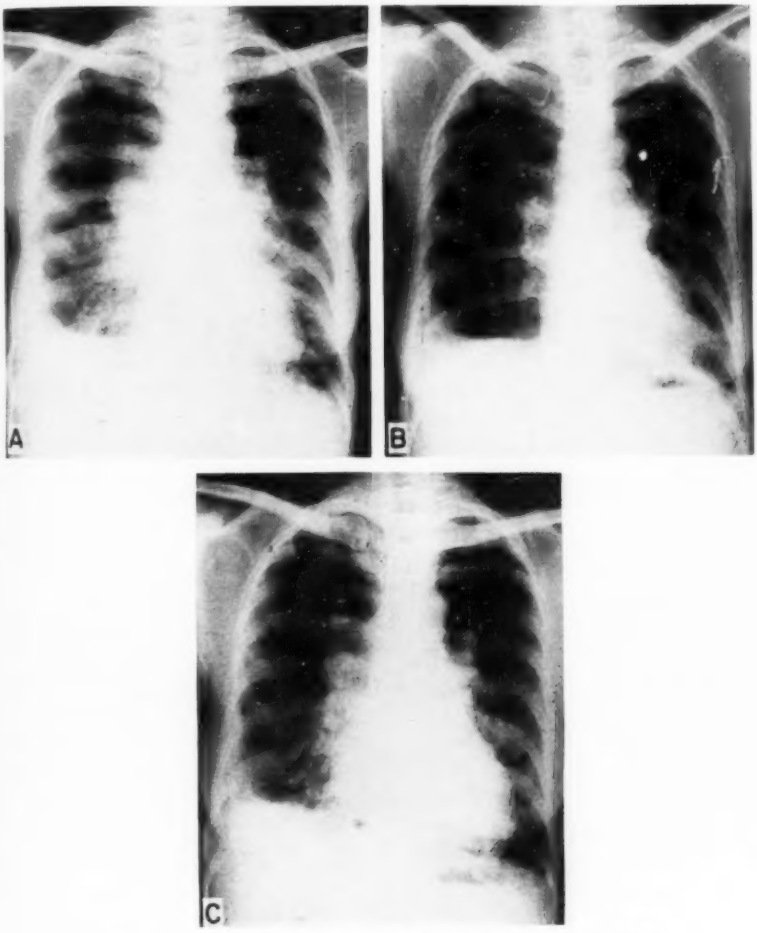

FIG. 2. Patient (1) L. W. Sarcoidosis, treatment with ACTH.

A. Before treatment. Bilateral hilar masses are seen, and there is a finely mottled, diffuse infiltration involving both lung fields. There is obliteration of the right costophrenic angle by either fluid or thickened pleura.

B. Chest x-ray taken on 17th day of treatment. There has been extensive clearing of the pulmonary lesions.

C. Film taken 25 days after *B* and eight days after treatment with ACTH was discontinued. The pulmonary infiltration is definitely greater than in *B*, but not as extensive as in the pre-treatment period.

condition was most striking. Within a very few days there was dramatic improvement in the ocular manifestations and these cleared up completely before the end of the period of therapy.

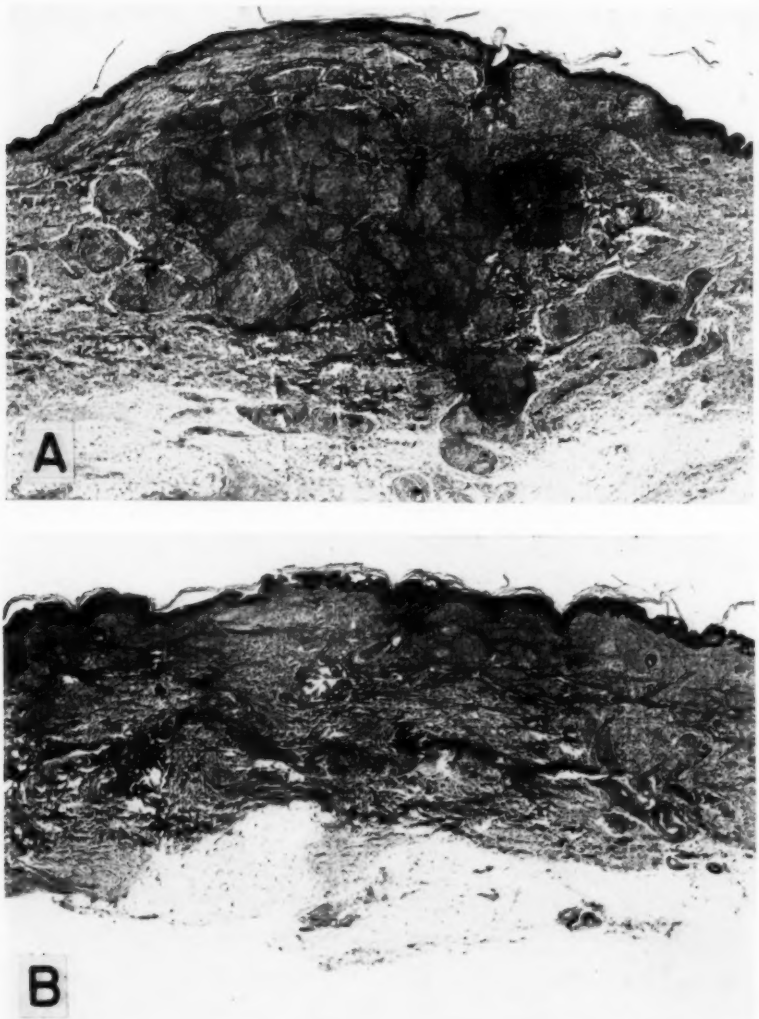

FIG. 3. Patient (1) L. W. Sarcoidosis treated with ACTH. Biopsies of cutaneous lesions.

A. Biopsy before treatment showing clusters of epithelioid tubercles beneath the dermis (see text).

B. Biopsy taken 35th day of treatment. Before treatment lesion in this area had the same appearance and was the same size as that in *A* (see text).

The skin lesions disappeared completely leaving no area of depigmentation or evident scar. The spleen could no longer be felt by the end of the period of treatment and the liver de-

creased significantly in size. The patient's marked pulmonary insufficiency improved remarkably both subjectively and by objective tests. Her vital capacity doubled and her maximal breathing capacity more than tripled over the control value. At the time of admission she could hardly move about due to marked exertional dyspnea but within two weeks after the start of therapy she was up and about the ward doing minor tasks without anv appreciable discomfort. The marked tachycardia gradually subsided.

It is interesting that some changes were noted within 48 hours after the onset of treatment. Her vision was less blurred. The fundus of the left eye could be visualized with ease

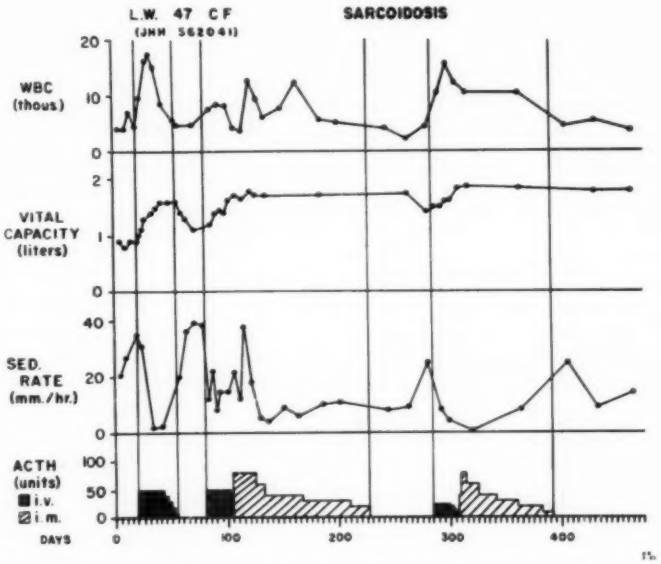

CHART 1. Patient (1) L. W. Sarcoidosis treated with ACTH. This chart shows the clinical course of this patient with sarcoidosis over a period of almost 16 months during which time three separate courses of ACTH were given. The effectiveness of the adrenal stimulation is reflected in the curve of the total white cell count and in the sedimentation rate while the functional change associated with the pulmonary lesions is depicted by the vital capacity measurements. Fairly severe relapses occurred promptly after each of the first two courses of treatment but the disease has remained quiescent since the third course except for a transient mild flare-up in the iritis.

by that time and the scleral and conjunctival injection had almost completely disappeared. The skin lesions definitely had a more flattened appearance. By the third day, her vital capacity was increased slightly having risen from 900 to 1050 cc. The patient noted that her breathing was easier and the difficulty was less accentuated with movement. By the fourth day the vital capacity was 1150 cc., the spleen was difficult to palpate, and the skin lesions were very definitely much flatter and softer. By the sixth day it was noted that the parotid swelling had decreased but there was no striking change in the size of the lymph nodes which were not much enlarged at the start. At the end of the first week of treatment the corneal

opacities were less evident. The fundus of each eye was seen with ease. Skin lesions were practically flat and might easily have been missed on examination except for the pigment changes. The objective signs in the lungs and the size of the liver had not changed further. The vital capacity had risen to 1300 cc.

By the end of the second week of treatment the change in exercise tolerance was very easily detected by both the patient and the physician. Her vital capacity had increased from 900 to 1500 cc. On the seventeenth day it was noted that the chest was clear on physical examination (Fig. 2*B*), the eyes were entirely normal and the skin lesions were no longer visible. At that time the liver edge was just palpable and the spleen could not be felt.

On the 35th day of treatment ACTH was discontinued, the dose having been reduced gradually down to 10 mg. per day. At that time the vital capacity was 1625 cc. The lungs were clear to percussion and auscultation. The skin (Fig. 1*B* and 3*B*) and eye lesions had disappeared and the liver and spleen could not be felt. Certain of the laboratory studies had altered significantly. The sedimentation rate had dropped to 2, the percentage of circulating monocytes had fallen from 24 to 4, the bromsulfalein retention was now 0.4 mg. having been 2.0 mg. before treatment, and the thymol turbidity reaction had dropped from 10 to 3.4 units.

On March 31, five days after discontinuing the ACTH, there was a return of some activity in the uveitis and the vital capacity had fallen to 1400 cc. (Fig. 2*C*).

The patient was again seen April 17, 1951 at which time she noted redness and marked photophobia of the left eye. In view of the severity of the recurring uveitis she was readmitted for further treatment with ACTH. The skin lesions had reappeared in the same areas. The left eye showed pericorneal injection. There were mutton-fat deposits on the posterior surface of the cornea, and iris nodules were described as well as a positive aqueous ray. There was no significant enlargement of the superficial lymph nodes. Loud crackling rales were heard posteriorly at both lung bases. The liver extended two fingerbreadths below the costal margin in the midclavicular line, but the spleen was not palpable. She was again quite dyspneic on the slightest exertion. The vital capacity had returned to its previous level of 900 cc.

On April 19, 1951 the administration of ACTH in the same dosage was resumed. The time course of the response of the sarcoid lesions was essentially similar to that noted during the first course of treatment. However, although her dyspnea subjectively improved there was not as marked improvement in some of the pulmonary function tests as during the previous course. On May 15, after 26 days of intravenous ACTH, she was shifted to 40 mg. of ACTH in sesame oil intramuscularly every 12 hours. Two days later she developed a temperature of 103° and it was noted that the site of injection of the sesame oil was free of any local reaction. She continued to run a low grade fever and the spleen again became palpable. By May 20 she complained of soreness of the buttocks. There seemed to be a slight exacerbation in the sarcoid lesions, and it was felt that the patient was not getting a proper degree of adrenal stimulation. Consequently she was shifted to beef ACTH 20 mg. in aqueous solution intramuscularly every six hours. Further improvement soon became obvious, as evidenced by a prompt fall in the sedimentation rate (Chart I), as well as by prompt regression of the reactivated lesions. On June 3 she was shifted to Acthar gel receiving 30 mg. intramuscularly twice daily. This was gradually reduced until she was receiving 40 mg. once daily intramuscularly at the time of her discharge from the hospital on June 12, 1951. At the time of discharge the vital capacity had reached 1730 cc. which was the largest recorded in this patient.

She was followed in the out-patient clinic and on July 16 the dosage of ACTH was lowered to 30 mg. of the gelatin preparation daily. When examined on June 30 there were no cuta-

neous lesions. The eyes appeared normal. The lungs were clear to percussion and auscultation and the liver and spleen were not palpable. She was next seen on August 13, 1951 at which time she was still taking 30 mg. of the gelatin preparation each day. There was no evidence of reactivation of any of the lesions nor evidence of any untoward effect of the ACTH.

On August 28 the dose was reduced to 20 mg. each day and finally administration was stopped on September 16, 1951. Three days later the patient noticed some evidence of inflammation and blurring of vision in the left eye. When seen on September 25 there was some improvement and by October 2 no signs of activity of the uveitis could be detected. She then got along quite well with no difficulties until November 1, 1951 at which time she developed photophobia and blurring of vision of the left eye again. Examination on November 5 revealed a very active uveitis with mutton-fat deposits, iris nodules and a positive aqueous ray. There was a plaque on the inner aspect of the left upper eyelid. The parotids were slightly enlarged and nodular. Small posterior cervical nodes were palpable. There were crackling rales during inspiration at both lung bases. The liver was easily palpable and radiological examination of the chest showed increase in both the enlargement of the hilar nodes and in the parenchymal infiltration. Pulmonary function studies done at this time did not show any decrease and were the same as the best achieved on ACTH. The eye lesions continued to increase in severity. The liver grew larger, and it was decided to readmit her on November 19 for further treatment with ACTH.

By the time her third course of ACTH was begun on November 27 the vital capacity had decreased to 1400 cc. From that date she received 25 mg. of ACTH daily in 750 cc. of 5% glucose. Again she showed a very prompt clearing of the media of the left eye and vision improved within a very few days. Regression of the skin lesions was as rapid as previously. On December 11 the dose of ACTH was reduced to 20 mg., on December 13 to 15 mg., and on December 15 to 10 intravenously. She was then placed on Acthar gel 40 mg. intramuscularly twice daily and discharged. At that time her vital capacity had again reached 1700 cc.

After her discharge on December 20, 1951 she continued 80 mg. of the long-acting ACTH daily for seven days and then 60 mg. for 11 days. She was examined on January 7, and no evidence of reactivation of the disease could be made out. The ACTH dosage was reduced to 40 mg. each day. At that time she was able to walk two miles on the level without dyspnea. On January 21 no exacerbation of any of the manifestations was noted. The ACTH was reduced to 30 mg. a day. Her condition remained good at the time of examination on February 26. The ACTH was reduced to 10 mg. daily for ten days and then therapy was discontinued. When seen on March 31, the sedimentation rate had become slightly elevated and the thymol turbidity was again above normal, but there were no other evidences of reactivation of her disease. At the time of her visit on April 20 the left eye was red and vision was very slightly blurred; otherwise she was asymptomatic. Eye manifestations increased and were brought under control by the local use of cortisone ointment. At the time of her last visit on May 26, 1952 the skin was clear, the lymph nodes and parotids were not enlarged. Liver and spleen were not palpable. Vital capacity was still at its maximum level and none of the other laboratory studies indicated any reactivation of the disease. After two weeks on the cortisone ointment this was discontinued, and there was no return of her eye difficulties.

The patient has been followed for 16 months during which time she received three intensive courses of treatment with ACTH. After the first two she had a prompt relapse but since the third the disease has remained quiescent except for a mild and transient flare-up of the iritis.

A brief description will now be given of the clinical course of the other patients during and after treatment:

In Case 2 (See Table I) the clinical manifestations were chiefly the result of respiratory tract involvement with orthopnea, dyspnea, night sweats and advanced changes on roentgenological examination. Of particular interest were the rows of sarcoid nodules along the palpebral margins. This patient was treated also with ACTH intravenously receiving a total of 1650 mg. over 39 days. The response was prompt and striking both subjectively and objectively and six weeks after the termination of the treatment she was entirely asymptomatic. She could ride a bicycle at least two miles without any shortness of breath.

In Case 3, who was treated very early in the study there was also severe respiratory involvement with dyspnea at rest and cough. In addition this patient had a rather striking hypercalcemia and severe renal insufficiency. His first course of ACTH consisted of 100 mg. a day intramuscularly over a seven day period. Even with this small amount of treatment there was disappearance of his respiratory symptoms and a striking fall in serum calcium to normal. He had a definite exacerbation of his disease four weeks after treatment was terminated but managed to return to work for eight months and then entered the hospital again because of severe dyspnea on exertion and cough. At that time he was given 100 mg. of cortisone daily for 14 days. Both the respiratory symptoms and the calcium abnormality responded well and just as fully as during the first course of treatment with ACTH. However, the improvement was less prompt. After this he returned to work as a laborer for six months and was asymptomatic until just 12 days before his third admission when he developed severe uveitis and recurrence of his cough. This time the predominant clinical manifestation was the uveitis; the respiratory symptoms being milder than previously. The renal insufficiency had not changed significantly in degree. This time he again received ACTH intramuscularly 100 mg. each day for seven days and for the third time there was a prompt and striking response. At the end of seven days treatment he was changed to ACTH by the intravenous route 40 mg. a day. His improvement continued, and there was also suggestive improvement in his renal function. The ACTH was gradually reduced over a period of 17 days. After this course of treatment he was able to work for nine months without return of difficulty and two weeks before his fourth admission ocular symptoms and dyspnea returned. Examination revealed again that the most important abnormality was severe bilateral uveitis. He was treated with ACTH intravenously over a period of one month during which time his uveitis became inactive and the serum calcium returned to normal. There was again suggestive improvement of renal function, but the results of the tests were difficult to interpret. He has not returned since discharge on April 25, 1952.

It is of interest that both Cases 1 and 3 had severe pulmonary difficulties at the beginning, but following repeated courses of ACTH there was less tendency for respiratory manifestations to be bothersome and uveitis became the prominent feature.

In Case 4 the predominant problem was again respiratory involvement with moderately severe extertional dyspnea, morning cough, and advanced changes in the chest roentgenogram. The patient also had uveitis which, however, was relatively mild. She received intravenous ACTH over a period of 33 days to a total of 1350 mg. Her clinical response was very prompt and striking, as far as both the uveitis and respiratory difficulties were concerned. She also had very extensive, slightly elevated, oval, pigmented cutaneous plaques over the

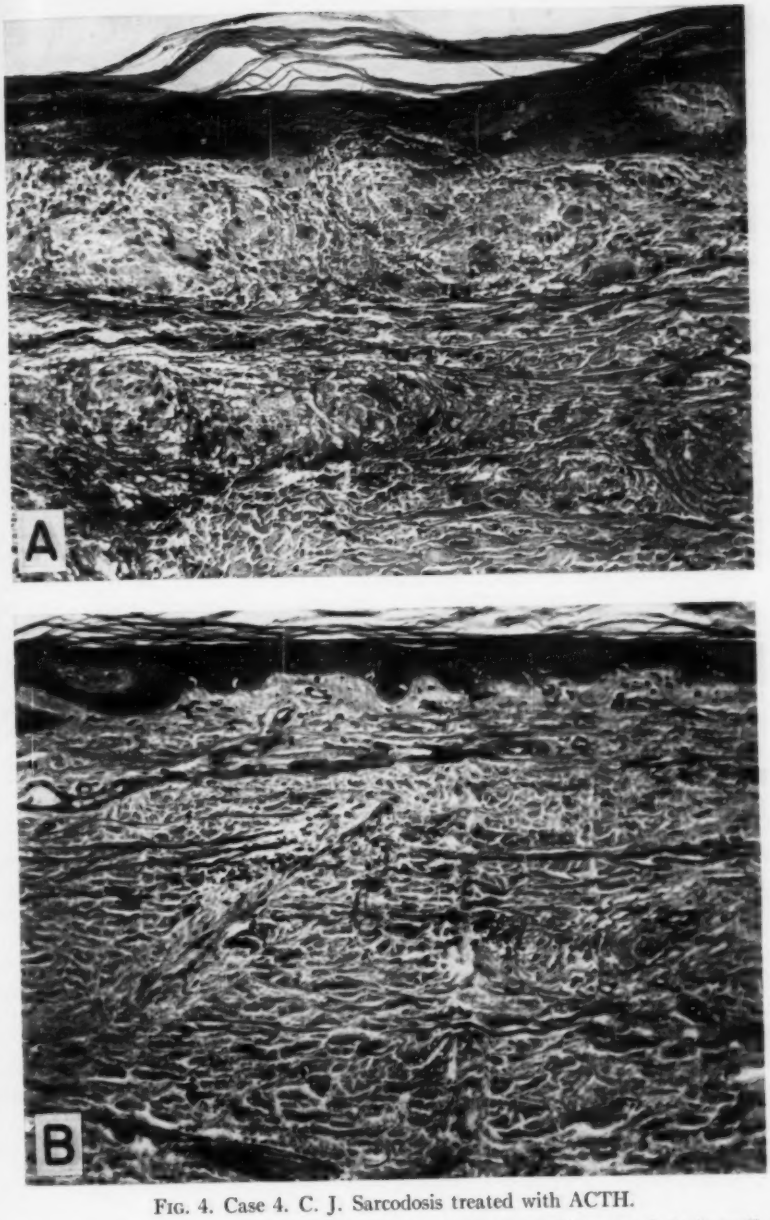

FIG. 4. Case 4. C. J. Sarcodosis treated with ACTH.

A. Biopsy of skin before treatment. Hard tubercles are seen which are relatively acellular. The cells seem to be more separated than in more advanced lesions. No neutrophils and only a few lymphocytes and giant cells were seen.

B. Biopsy of smaller lesion as in *A* taken on 18th day of treatment. Only a few epithelioid cells and no giant cells are seen. Diagnosis of sarcoidosis could not be made from this picture.

lower extremities (Fig. 4*A*). Biopsy showed nests of epithelioid tubercles beneath the dermis. During treatment the lesions flattened, there was desquamation and the skin became smooth and normal in appearance (Fig. 4*B*). However, beginning two weeks after cessation of treatment there was a very rapid exacerbation of her difficulties which reached a maximum at four weeks and then slowly subsided over the next few weeks to reach an asymptomatic state. She has since been followed for one year and has been at work with no exertional dyspnea and no symptoms related to the eyes.

Case 5 also had had progressive severe exertional dyspnea accompanied by marked weight loss and showed severe renal insufficiency and hypercalcemia. The patient was also treated early in the study and received ACTH intramuscularly 100 mg. daily for his initial dose with reduction over 11 days to a total of only 700 mg. However, there was prompt and striking improvement in the dyspnea and the serum calcium fell to normal. Since that time he has been asymptomatic, worked for 18 months, gained 70 pounds in weight and plays 18 holes of golf without dyspnea or fatigue.

Case 6 also had severe exertional dyspnea with very advanced changes on x-ray examination (Fig. 5*A*). There was a pleural effusion which had required repeated thoracenteses. This patient also had uveitis of moderate severity and extensive dermal lesions. A moderate degree of loss of weight was noted. He received ACTH intravenously with an initial dose of 50 mg. Treatment was continued over 42 days and a total of 1550 mg. was given. Improvement again was prompt and striking. The pleural effusion disappeared without further removal of fluid being necessary (Fig. 5*B*). The uveitis subsided and all of the dermal lesions as well. One year after this course of treatment the patient was still asymptomatic, could walk at least 20 blocks without any dyspnea, and there was no recurrence of the pleural effusion (Fig. 5*C*).

In Case 7, the remaining patient who had predominant respiratory involvement, the problem was complicated by rheumatic heart disease with mitral stenosis and insufficiency and aortic insufficiency. The patient was very severely dyspneic, and there were audible wheezes throughout the chest. Fever was also present. Radiological studies showed extensive lesions of sarcoidosis and a lymph node biopsy confirmed the diagnosis. He was begun on ACTH, at first 50 mg. intravenously, daily, and later in decreasing doses over 28 days to receive a total dose of 1200 mg. There was very considerable improvement both subjectively and objectively, but recurrence of symptoms began within one week of stopping the drug. A second course of ACTH intravenously was then administered with an initial dose of 40 mg. decreasing over 12 days with a total dose of 480 mg.. There was evidence of pulmonary insufficiency which was thought to be attributable mainly to the sarcoid infiltration of the lungs. However, treatment had to be stopped at the end of 12 days because of weight gain of 18 pounds and obvious clinical evidence of congestive heart failure. There had been prompt symptomatic improvement as far as the pulmonary manifestations were concerned, however, which became evident even after the first intravenous infusion. The patient died at home one month later in acute pulmonary edema. No post-mortem examination was made.

In three patients the major problem was related to the eyes.

In Case 8 there was a very severe uveitis and also evidence of retinal involvement with marked edema and clouding of the vitreous of the left eye. There was very marked diminution in vision. From the description by the ophthalmologist it seemed clear that this was a

granulomatous iritis of the type seen in sarcoidosis. She was first given intravenous ACTH with an initial dose of 30 mg., treatment extending over 21 days with a total of 540 mg. being

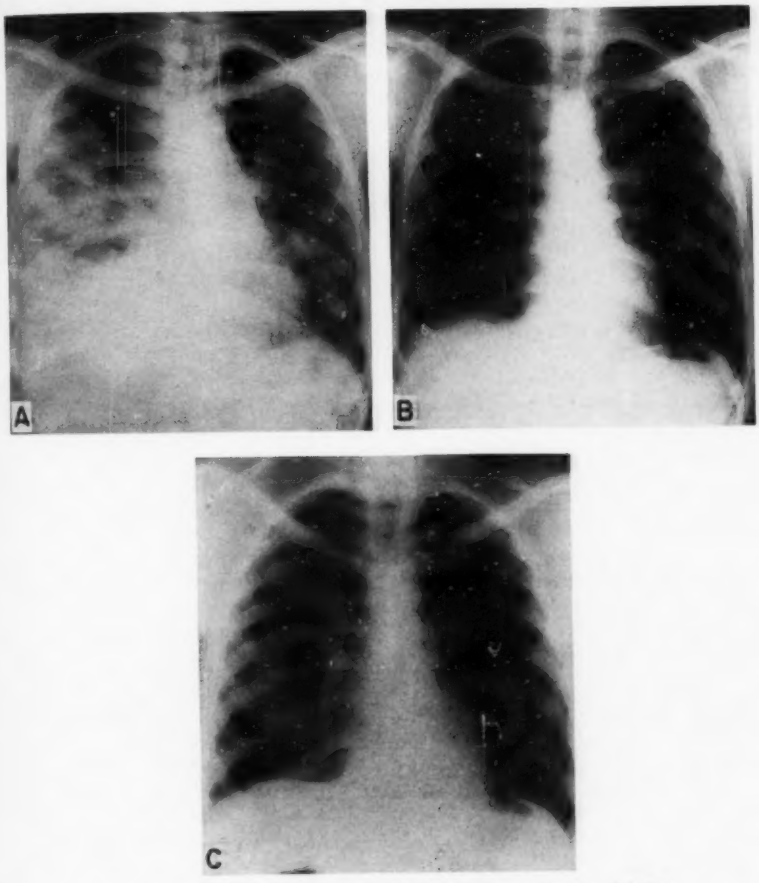

FIG. 5. Patient (6) A. H. Sarcoidosis, treatment with ACTH

A. Before treatment. There is a patchy mottled infiltrate involving both lung fields. On the right, there is a rather large pleural effusion which extends upward to the level of the clavicle along the lateral chest wall and obscures the lower third of the right lung field.

B. 23rd day of treatment. There has been extensive resolution of both the bilateral parenchymal infiltration and the right pleural effusion.

C. 11 months after treatment. Essentially similar to *B*. Improvement has been maintained.

given. The response was very prompt and striking with almost complete clearing of the eye. However, three weeks after discontinuance of treatment there was a recurrence at which time she was given cortisone eye drops with disappearance of all evidence of activity within

one week. Six weeks later there was a second recurrence, and she was again treated with intravenous ACTH, receiving an initial dose of 30 mg. with a total dose of 375 mg. over 14 days. Again there was a prompt and complete clearing of the active lesions. Following this she was placed on ACTH in gelatin intramuscularly beginning with 100 mg. daily and gradually tapering to 40 mg. Treatment extended over 36 days with a total dose of 1890 mg. During this whole period her ocular improvement was maintained. Treatment was stopped because of her intolerance to the injections locally. Within two weeks a mild recurrence was evident. It was thought at this time that the activity should be kept under control to prevent permanent loss of vision from the inflammatory reaction. Consequently she was placed on cortisone beginning with a dose of 200 mg. daily decreasing gradually down to 25 mg. a day which was continued over a period of six months. Again the activity of the uveitis subsided very rapidly and the patient has not received cortisone for six weeks with no evident recurrence having taken place in that period of time.

Case 9 had severe bilateral uveitis (Fig. 6*A*) and intradermal and subcutaneous nodules as well. Before being seen at this hospital he had been treated with ACTH intramuscularly, 50 mg. daily for nine days. There was questionable, if any, improvement in his condition. In addition, he had been given two courses of urethane with only questionable improvement. Shortly after admission to the hospital ACTH was begun by intravenous injection with an initial dose of 50 mg. a day. Treatment was continued over a period of 17 days, a total dose of 750 mg. being given. The activity of the uveitis subsided very promptly and completely (Fig. 6*B*) and there was rather remarkable improvement in the skin and subcutaneous lesions as well. After ACTH was discontinued, he was immediately placed on cortisone ophthalmic ointment and the uveitis has remained inactive over a period of eight months. At the end of this period, however, a mile episcleritis was noted by the ophthalmologist. The cutaneous lesions have remained quiescent.

Case 10 had far advanced bilateral uveitis. Previous treatment with urethane had resulted in slight improvement in the right eye. The left eye showed much scarring, but there was still evidence of active disease present. The patient was begun on intravenous ACTH (beef) at 40 mg. a day. He exhibited resistance to high doses and the daily amount was raised to 60 mg. There was no satisfactory response and the pork ACTH was utilized. He was treated over a period of 37 days receiving a total of 1910 mg. After changing to pork ACTH the uveitis in the left eye became completely quiescent. One month after the cessation of treatment there was evidence of slight recurrence of active uveitis and when the patient was seen seven months after treatment this was even more marked and local therapy was begun with cortisone.

Case 11 had very little in the way of active lesions at the time treatment was started. There was ptosis of the right upper lid with a bandlike mass palpable. On biopsy this showed extensive fibrosis with epithelioid tubercles scattered through the connective tissue. The patient was treated with cortisone by mouth, 200 mg. daily initially. Treatment was continued over 23 days, a total dose of 3125 mg. being given. There was slow reduction in the size of the lesion which did not completely subside, however, and two weeks after treatment had been stopped it was slightly larger in size again.

This case seems consistent with the conclusions of others that old lesions in which considerable healing and fibrosis has already taken place do not respond very dramatically. Also this patient did not have what might be considered very intensive therapy in comparison to others in the present series.

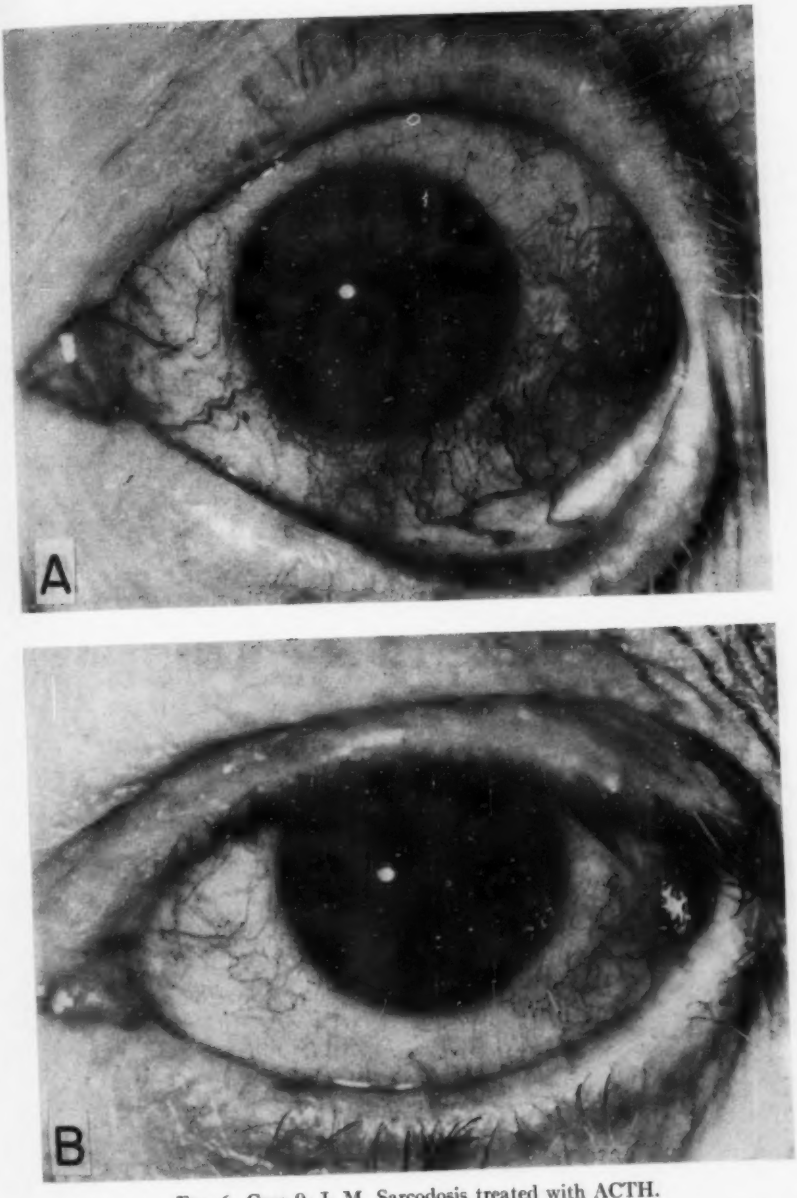

FIG. 6. Case 9. J. M. Sarcodosis treated with ACTH.

A. Left eye before treatment. Note cloudy appearance of the cornea and the pericorneal and conjunctival injection.

B. Left eye on 16th day of treatment. The eye is white and the cornea is clear.

Two patients were of interest because of the presence of gastrointestinal symptoms, striking enlargement of the liver and spleen and marked elevation of the alkaline phosphatase activity of the blood.

Case 12 complained of marked loss of weight, pain in the right upper quadrant with a feeling of fulness in the epigastrium and anorexia. There was also a moderate degree of exertional dyspnea. There was marked enlargement of both the liver and the spleen. Laboratory studies showed alkaline phosphatase activity of 46 Bodansky units and bromsulfalein retention of 1.9 mg. in 30 minutes. The patient was started on 40 mg. of intravenous ACTH daily, treatment being continued over 23 days with a total dose of 700 mg. Within one week all of her abdominal symptoms had disappeared and the liver and spleen were much smaller in size. Her dyspnea had abated. Over the three-week period of treatment the alkaline phosphate activity had dropped progressively to 16.4 Bodansky units. One week after treatment was discontinued evidences of a beginning recurrence were noted and the alkaline phosphatase activity began to rise, but when she was seen 10 weeks after treatment had been stopped she was still asymptomatic, had regained eight pounds in weight and was still a great deal better than before treatment.

Case 13 had far advanced bilateral uveitis which was quiescent on the right but mildly active on the left. The striking feature was marked enlargement of the liver and spleen with alkaline phosphatase activity of 31 units. This patient also had marked wasting and muscular weakness and on examination of the biopsy specimen marked infiltration of the muscle by the lesions of sarcoidosis was seen. The patient was essentially blind in both eyes and it was not expected that there would be much improvement because the changes were those of scarring and thought to be irreversible. However, considering the limitations, response to treatment with intravenous ACTH was very gratifying. An initial dose of 25 mg. per day was given, treatment was continued over 28 days with a total dose of 600 mg. The uveitis in the left eye became quiescent. The alkaline phosphatase activity dropped within 17 days to 7.3 units and there was definite but gradual and progressive improvement in muscle strength. There was also a striking reduction in the size of the liver and spleen. Two weeks after treatment there was evidence of a partial relapse with a rise in alkaline phosphatase activity to 19. However, the improvement in muscle strength was maintained during that period.

The remaining two cases presented certain rather unusual features.

Case 14 had fulminating sarcoidosis which presented in a rather bizarre manner. Initially there was high fever and extensive erythema nodosum. She also had a moderate degree of uveitis bilaterally and although there were no pulmonary symptoms, radiological examination revealed pulmonary infiltration and enlargement of the hilar nodes. She was treated first with intramuscular ACTH, starting with a dose of 100 mg. a day. Treatment extended over 18 days with a total dose of 1400 mg. The lesions of erythema nodosum disappeared rapidly and the activity of the uveitis subsided within a few days. She felt better in every respect but, beginning about six weeks after discharge, evidence of progressive pulmonary involvement was noted. No special treatment was given at this time and when she was seen five months after the first course of ACTH, some improvement was noted. Shortly after this, however, her ocular manifestations became active again, and she developed numerous small nodules over the legs and arms and was readmitted for further treatment. She was given ACTH intravenously with an initial dose of 30 mg. a day. She received the drug for 13 days to a total dose of 390 mg. The uveitis cleared rapidly and there was improvement in pulmonary function and a reduction in the size of the subcutaneous nodules. However, the

patient became sensitive to the beef ACTH and treatment was interrupted. Following this there was prompt relapse in all of the areas involved. It was then decided to treat the patient with urethane, and after a long period on this drug there was moderate improvement in the activity of her disease.

Case 15 had hypercalcemia, rapidly advancing renal insufficiency and a cerebral lesion with right hemiparesis. The patient was very critically ill. He was given ACTH intramuscularly 100 mg. a day. Treatment was continued for nine days for a total dose of 720 mg. The serum calcium dropped promptly to normal. There was no evident improvement in renal function. Treatment was stopped because of the deteriorating mental status of the patient. He died 10 days later at home and a post-mortem examination was done which showed extensive lesions of sarcoidosis, all of which were in an inactive state. The kidneys exhibited the changes seen in nephrocalcinosis without evidence of infiltration with sarcoid.

These descriptions of the effects of ACTH and cortisone on sarcoidosis give evidence that they suppress the activity of the disease if administered in adequate doses. Even in those cases treated with repeated courses over long periods of time no evidence of active tuberculosis has been discovered. The course of the disease after treatment has been of interest. Reactivation of the disease has been irregular and the subjective manifestations have not always paralleled objective measurements of function. The natural course of the disease is characterized by an irregular progression with remission and exacerbations, and the results after treatment seem in keeping with this natural progression. Since the development of the disease and its progression is so variable from patient to patient and from the point of view of areas involved, it seems worthwhile to analyze more fully the effects of treatment on these localized manifestations.

Constitutional Manifestations

In view of the extent of the involvement in many cases of sarcoidosis the infrequency with which severe constitutional manifestations develop is remarkable.

Loss of weight may be a distressing feature of the disease. The average loss of weight in the present series of cases over the twelve month period preceding treatment was 25 pounds. Eleven of the 15 patients lost from seven pounds over a two month period up to as much as fifty pounds in three months.

Reversal of this trend occurred in eight of the 11 patients during and after ACTH administration, four regaining their normal weight. The most striking example was patient J. E. who had lost 55 pounds prior to hospitalization. During treatment he gained 13 pounds, then lost three in the immediate post-treatment period, but over the past 17 months he has again reached his normal weight. In contrast, patient J. C. who also lost 50 pounds before treatment has only been able to maintain himself at this level in spite of four courses of ACTH or cortisone given over the past 30 months.

Eleven of the 15 patients exhibited fever prior to treatment. In nine it was

very mild in degree and usually somewhat irregular. In the other two the rectal temperature was higher, ranging from 100° to 102°F. Complete defervescence occurred in all patients during treatment. This was usually prompt, occurring within the first 24 hours in seven patients. In the other four, fever had disappeared after 2 to 5 days.

During the immediate post-treatment period it was common to note the reappearance of fever usually to the degree recorded prior to treatment. This occurred in nine of the 11 patients. In two instances, however, fever higher than that seen prior to ACTH administration developed. This appeared to be a "rebound" phenomenon, for within a period ranging from a few days to four weeks the temperature fell to normal in six patients and to levels below those seen prior to ACTH in the other two.

Moderate tachycardia (90 to 120 beats per minute) was also a common finding, being recorded in nine cases. During ACTH or cortisone, there was a fall in the pulse rate in all patients, the average being approximately 20 beats per minute. The reduction in tachycardia began between the first and the sixth day and was maximal between the second and the ninth day of treatment. The pulse rate increased during the immediate post-treatment period in all patients usually to the pre-treatment level. In four cases the recurrent tachycardia persisted, but in the other five it generally subsided within a month.

Ocular Involvement

The incidence of sarcoidosis of the eye varies in different series of cases. Uveitis is most commonly seen but there may be lesions of the eyelids and lachrymal glands, conjunctivitis, episcleritis, chorio-retinitis, hemorrhagic retinitis, cataracts, glaucoma and optic atrophy (1).

The ocular manifestations of sarcoidosis were extremely prominent in this group of patients. Owing to the possibility of irreversible visual loss every effort was made to bring about a suppression of activity in these ocular lesions. Thirteen of the 15 patients had some variety of ocular involvement. In many patients more than one variety of lesion was present. Defective vision was the chief presenting complaint in seven patients; prior to the first course of ACTH in four patients and prior to subsequent courses in three others.

Nine patients exhibited active uveitis of varying severity. Although most of the patients had only had symptoms for a few months at most, two patients had had for at least one year fulminating and far advanced disease which had produced irreversible scarring. There was bilateral involvement in seven cases; unilateral in two. Under therapy seven patients exhibited complete clearing of the signs of active uveitis and one had partial suppression of activity. The typical course of events included clearing of the periocorneal injection, dis-

appearance of the positive aqueous ray, absence of fresh, newly-formed keratitic precipitates, Koeppe nodules and iris nodules, with clearing of the vitreous opacities and nodules by the end of the first week. Visual acuity was usually much improved at this time. During the second week, disappearance of the keratitic precipitates, resolution of the iris and vitreous nodules and further clearing of the vitreous opacities were observed, so that by the end of the second week virtually all signs of activity had disappeared. During the two weeks after the conclusion of therapy, the uveitis returned to its pre-treatment severity in one patient, partially returned in two patients and remained unchanged in five patients. Two of the last group, however, subsequently relapsed to the severity noted before treatment.

Four patients have been treated repeatedly for recurrent attacks of uveitis at the first sign of appreciable activity. In two patients after relapse following the first course, the second course was extended over two to four months by the use of long-acting ACTH in slowly reduced doses. Both of the patients relapsed following this more protracted course and a third protracted course—ACTH over four months in one patient and cortisone over six months in the other—were given. After discontinuing the ACTH in the first patient a moderate relapse occurred at six weeks, but this was successfully handled by the prompt application of cortisone ophthalmic ointment. The second patient has not been given cortisone for the past six weeks and the eyes have remained completely quiescent. Two patients had appreciable remissions lasting in one for seven and nine months respectively after each of two courses of ACTH and in the other patient for six months after one course of ACTH. However, in the former patient during the third course severe glaucoma, which had cleared during the second ACTH course persisted and it was necessary to employ ocular paracentesis, which relieved the situation only temporarily. A mild recurrence occurred in the latter patient four weeks after the second course of ACTH was completed.

One patient after inactivation of uveitis during a course of ACTH was placed immediately on cortisone ophthalmic ointment and this was to be continued indefinitely. When seen eight months later no sign of active uveitis could be detected, but he had developed scleritis and episcleritis not previously noted.

Two other patients with far advanced uveitis were given ACTH. Severe disease had been present in both patients for more than one year prior to admission. Vision was 1/200 in the affected eye in one patient and only hand movements were seen bilaterally by the other. With the realization that the chances of improving vision in these patients were very slim, the presence of signs of moderately active uveitis prompted the institution of ACTH administration as a desperate measure. Although the signs of activity disappeared during ACTH in these patients, vision was in no measure improved.

Of five patients with active retinitis, inactivation occurred in four patients within two weeks after initiating therapy. Relapse occurred in three patients between three weeks and nine months after concluding therapy.

Conjunctival nodules seen in one patient began to recede on the twelfth day of ACTH and were gone on the seventeenth day. They have not reappeared during the subsequent year.

Eyelid lesions were seen in three patients. In two the lesions consisted of small discrete nodules (1–5 mm. in diam.) mostly near the lid margins; in the third patient large, elevated, slightly nodular plaques were present on all lids. There was a tendency towards medial concentration of the lesions. In each case the lesions were decidedly smaller and flatter by the end of the first week and were gone by the end of the third week, leaving no stigmata of their prior existence. There was a partial recurrence in two patients, three and six weeks after ACTH adminstration. One of these has been retreated with ACTH without evidence of relapse three months after therapy.

One patient presented with unilateral ptosis of the right upper eyelid of three weeks duration. On examination, through the edematous lid a firm, elongated (15 x 3 mm.) mass was palpated and presumed to represent dacroadenitis. However, exploratory operation revealed the mass to be distinct from the lacrimal gland and biopsy revealed dense fibrous tissue in which small epithelioid tubercles were imbedded. On 200 mg. cortisone daily by mouth the mass slowly regressed over a 16-day period to one-half of its former size and the ptosis partially receded. Continued treatment resulted in no further improvement.

In summary, therefore, ACTH and cortisone appeared to be capable of inducing striking inactivation of the lesions of acute sarcoid uveitis. If treatment was instituted in the early phase of the process, restitution of vision was usually effected. If, on the other hand, considerable scarring had resulted from long-continued activity over several months, little, if any, improvement in vision was observed, in spite of the suppression of activity of the uveitis. The tendency toward relapse was great and at times vigorous, long-continued application of the hormone was needed. There was a suggestion in two patients that the topical application of cortisone ophthalmic ointment was helpful in suppressing anterior uveitis.

Lungs

The pulmonary manifestations of sarcoidosis are protean and may take the form of disseminated lesions, linear infiltration radiating from the hilar region, nodular infiltration or diffuse and confluent infiltration. Longcope and Freiman (1) have stressed that frequent transformations may occur in the type of lesion seen. They may remain unchanged for years, or not infrequently recede to the point of complete disappearance.

Pulmonary involvement occurred in 10 of the 15 patients in this group. The extent of the involvement varied a great deal, ranging from hilar lymph node enlargement alone without symptoms, abnormal signs on physical examination, or parenchymal involvement by x-ray; to severe widespread involvement producing dyspnea at rest, copiously productive cough, harsh crackling rales, pleural reaction with effusion, extensive x-ray changes in hilar nodes, parenchyma and pleura, and markedly reduced respiratory function as determined clinically and by physiological testing. In seven of these patients severe respiratory difficulty constituted the cardinal complaint prior to treatment.

Cough and dyspnea were the most frequent symptoms, being noted in eight patients. In some cases the cough was mild and occurred upon awakening whereas in others it was severe and constant throughout the day. In five the cough was productive of as much as one cup daily of sputum which was characteristically white and frothy. During treatment the cough disappeared in all patients between the third and fourteenth day. In four patients it has not reappeared after treatment. In two it has reappeared during the immediate post-treatment period only to disappear thereafter; and in two others it has reappeared at one and at nine months after conclusion of treatment. Dyspnea in these eight patients would occur at different degrees of activity: at rest in three patients; with slight exertion in three; and in two with moderate exertion. The relief from dyspnea during ACTH or cortisone was very impressive. In all patients breathing was decidedly easier by the third treatment day. In seven dyspnea, even on exertion, was relieved at some time between the first and twenty-first day of treatment; in one improvement continued during the first two weeks of treatment but no further change occurred thereafter. Following treatment there has been no recurrence of dyspnea in six patients who have been observed over three to seventeen months. In one dyspnea returned three weeks after therapy to its pretreatment severity whereas in another patient partial return occurred nine months after treatment. Three patients complained of orthopnea of one week to three months duration. After one week of treatment all three could lie flat without discomfort. Two continued to be able to lie flat with ease after treatment was stopped, whereas in one patient orthopnea reappeared two weeks after therapy. One patient complained of pleuritic pain prior to treatment. This disappeared after ten days of treatment and has not recurred. Thus, during the administration of ACTH or cortisone, symptoms even of the most severe degree entirely disappeared and following treatment a majority of the patients remained symptom free.

Abnormalities on physical examination of the chest were present in ten patients. Tachypnea, recorded in all ten prior to treatment, disappeared in nine and abated considerably in the tenth during treatment. Within one month after treatment the respiratory rate once again became rapid in six patients; in two of these it shortly returned to normal. In four tachypnea has not re-

appeared during the post-treatment period. Dry crackling rales were heard in four patients prior to treatment. The rales disappeared in all four as early as the first day and as late as the fourth week of treatment. Following treatment they recurred in all cases, promptly but transiently in two, promptly and persistently in one, and after a nine months remission in the fourth patient. Impairment of the percussion note, usually at the right base posteriorly, was noted in five patients before treatment. In three patients full resonance reappeared and in two patients the percussion note became less impaired during treatment, these changes being noted after one to three weeks. The chest in two patients has remained fully resonant during three and twelve months respectively after treatment. In summary, then, abnormal physical signs in most patients disappeared entirely during the administration of ACTH or cortisone. In roughly half the patients early relapse was observed but in some instances this relapse was only temporary. Many of these abnormal physical signs have not returned during the observation period which has been as long as 12 months.

Abnormal radiological findings were observed in 12 of the 15 patients. In two patients mediastinal lymph node enlargement alone was seen, whereas in the others there were also parenchymal and pleural changes. An evaluation of the x-ray findings was performed by Dr. David Gould of the Department of Radiology. The changes in the size of the mediastinal lymph nodes will be described in the section concerned with lymph nodes. Prior to treatment ten patients exhibited parenchymal infiltrations and pleural changes occurred in six patients. In eight of the ten patients the parenchymal involvement was severe. During treatment striking clearing of the miliary or nodular infiltrations were readily observed in seven of the ten patients. Clearing was not initially apparent before the end of the second week of treatment and not maximal in some patients until the end of the fifth week (Figs. 2 and 5). In the remaining three patients (Case 3—1st and 2nd admissions; Case 5 and Case 14, 2nd course) the duration of treatment was in no instance longer than two weeks. When one of these six patients (Case 3) subsequently was given longer courses of ACTH (24 and 30 days) considerable clearing was observed on both occasions. Another patient (Case 5) had only one x-ray examination on the eighth day of ACTH which showed no changes, but he obtained complete subjective relief of several months duration. The third patient (Case 14) exhibited signs suggestive of ACTH hypersensitivity during a thirteen day course and it is difficult to know the extent of adrenocortical stimulation induced by ACTH at that time. Clearing of the parenchymal infiltrations was in no instance complete during treatment, but in four patients the radiologist stated that he would not have suspected sarcoidosis from the films had he not had previous x-ray examinations for comparison. Following treatment, the parenchymal infiltration reappeared rapidly (within 2 weeks) in two

patients; in the others, there was only slight, if any, recurrence. Figure 2 shows the chest x-rays before treatment, on the 16th day of treatment, and eight days after treatment in Case 1. The extensive clearing of the parenchymal infiltrate and its rapid and partial recurrence is readily seen. On the other hand, Figure 5 which depicts the chest x-rays before, during, and ten months after the conclusion of therapy in Case 6 exemplifies the appreciable period of remission which may ensue. In addition to parenchymal abnormalities involvement of the pleura was seen in six patients. In five this consisted principally of pleural reaction with only slight, if any, effusion. One patient (Case 6), however, was demonstrated to have a massive pleural effusion, said to be a rare occurrence in this disease. Prior to treatment two thoracenteses were performed which removed 650 and 600 cc. respectively of pleural fluid which was sterile on both routine and tuberculous culture. Following each pleural tap a rapid reaccumulation of fluid occurred. During ACTH therapy the effusion gradually disappeared over a three week period without further thoracentesis (Fig. 5). There was reappearance of a small amount of fluid three weeks after therapy but none thereafter during the 12 month follow-up period. In the five patients with pleural reaction without effusion, there was slight clearing in three patients and no change in two.

Detailed pulmonary function studies were performed before, during and after treatment in seven patients (Table II). In all seven patients the vital capacity was below the predicted normal values based on the age and height of the patient. In all patients the vital capacity increased during treatment, this increase being as small as 320 cc. and as large as 1650 cc. In four patients this constituted a return to the predicted normal values. On the other hand, the maximal breathing capacity was below the predicted normal levels in only three of the six patients in whom this determination was made prior to treatment, but increased in five of the six patients during treatment; in the sixth patient it was above normal at the start. The ratio of dead space to tidal volume, expressed as a percentage, was greater than normal prior to treatment in all seven patients and was reduced by 2–17% during treatment. In four patients this change reduced the dead space percentage to within the predicted normal range. The ratio of venous admixture to total blood flow, also expressed as a percentage, was above normal in the six patients in whom it was determined prior to treatment. In four patients there was a significant decrease during therapy bringing two patients to within the normal range. There was no significant change in two other patients. The oxygen diffusing capacity increased only slightly in the three patients in whom it was measured. In four of six patients the arterial oxygen saturation was below normal; strikingly so in two patients at 83%. All returned to within the normal range (>95%) during treatment. During the follow-up period the vital capacity and the maximal breathing capacity either remained at the increased levels or

TABLE II

Measurements of Pulmonary Function

CASE NO.	COURSE NO.	VITAL CAPACITY				MAXIMAL BREATHING CAPACITY				DEAD SPACE RATIO				VENOUS ADMIXTURE RATIO				DIFFUSION CAPACITY				ARTERIAL OXYGEN SATURATION			
		N	B	D	A	N	B	D	A	N	B	D	A	N	B	D	A	N	B	D	A	N	B	D	A
1	1	2435	860	1630	1330	62	33	89	57	<30	51	40	43	<6		10		>10	3.3	5.5	—	95	83	95	
	2		1280	1750	1520		57	97	81		43	38	45		17	9	11		7.8	9.9	—				
	3		1520	1820	1790		81	103	84																
2		2950	2500	2860	2640	90	155	145	134	<30	36	22		<6	11	8						95	94	95	
3	1	4330	1930	3460	3500	126	104	155	134				38	<6											
	3		3690	4480	3970		134	166	148		40	38			20	7		>10	3.7	5.8		95	92	96	
	4		3250	4280			117	155															83	98	
4		2905	2300	3070	2430	87	—	153	117	<30	45	28	48	<6	13	3	15								
6		4440	2600	4250	4610	130	117	222	167	<30	30	22										95	91	97	
7		4070	2420	3070	2180	111	57	91	—	<30	33	25		<6	12	11		>10	7.3	10.0					
14		3260	1990	2310	2005	89	117	139	127	<30	49	44	53	<6	11	5	9					95	95		

N = Normal Value. B = Before treatment. D = During treatment. A = After treatment.

partially returned towards the pretreatment levels. The other measurements of function usually reverted promptly to pre-treatment values, although the data here are incomplete. In general, it was believed that the changes in the vital capacity correlated better with the changes in the patient's symptoms, signs and x-ray findings than did the changes in any of the other respiratory function measurements listed above. A detailed report of these changes in the pulmonary function tests during and after ACTH in three of these patients by Dr. R. L. Riley, Dr. M. C. Riley and Miss H. Hill forms the subject of an accompanying paper (17).

Skin

Ten patients in this series exhibited a wide variety of skin manifestations with more than one type of lesion being seen in four. Two patients had a very dry, finely scaling eruption, principally over the extensor surfaces of the extremities with moderate pruritus. In four, small (1–5 mm. in diameter) discrete, slightly elevated nodules were found on the forehead, eyelids, nose, ear lobe, neck and trunk. Larger (0.5–2.0 cm. in diameter), discrete, moderately elevated, yellow or pink, slightly lobulated, waxy, firm granulomata were found in three patients on the extensor surfaces of the elbows and knees, nape of the neck, nasal fold and eyelids (Fig. 1). Three patients had more extensive involvement with granular, scaling skin over wide areas including both the extremities and the trunk. The areas involved were usually only slightly elevated, frequently pigmented (silvery-brown) and there were shiny plaques measuring 0.5–1.5 cm. in diameter. Lastly, two patients exhibited both intradermal and subcutaneous nodules of varying size, principally on the lower legs and forearms, and one patient (Case 14) presented the classical picture of severe erythema nodosum involving the lower legs with red nodules and edema.

In nine of the 10 patients all of these various cutaneous manifestations entirely disappeared during the administration of ACTH or cortisone. The clearing of these lesions was one of the most striking changes noted in this study. Pruritus was usually gone by the third day and the dry scaling skin became moist and smooth. The small, discrete nodules were noticeably smaller as early as the second day in some patients, but in others the regression of the lesions took place more slowly, 28 days of ACTH administration being required in one instance to induce complete clearing of these lesions. The larger, more elevated granulomata were seen to be decidedly flatter as early as the third day and disappeared entirely in one to four weeks, leaving no traces of their prior existence such as scarring or pigment changes. In the four patients with the more extensive involvement, the skin became progressively softer, smoother and less thick, the plaques gradually disappeared and the shiny pigmented areas flaked off, frequently leaving depigmented areas in which

there was only slight, if any, scarring on subsequent examination. Subcutaneous nodules became impalpable in one patient and only barely palpable in the other patient.

In none of the patients did an exacerbation of the cutaneous lesions occur during the immediate (2 weeks) post-treatment period. Four patients have subsequently remained free of skin involvement during the post-treatment period of observation which ranges from six weeks to 18 months. Five patients have had gradual reappearance of lesions following remissions of one to nine months. The patient (Case 1) who had a remission lasting one month has been subsequently retreated with ACTH and was free of skin lesions three months thereafter. A full-blown exacerbation has occurred in one patient (Case 3) with the disseminated variety after each of three courses of ACTH or cortisone, although following the most intensive course a period of remission of seven months ensued.

Lymph Nodes

Enlarged, discrete, movable, rather firm, non-tender peripheral lymph nodes were palpable in 13 patients. In almost all of these patients more than one chain of nodes was involved. During the administration of ACTH or cortisone the affected lymph nodes could no longer be felt in 11 patients after seven to 16 days. In one case there was considerable reduction in the size of the nodes and in another patient the nodes remained unchanged. After discontinuing therapy, six of the patients remained free of adenopathy during the observation period; three had partial recurrences; two had complete recurrences; and in three the status of the peripheral lymph nodes is not known.

In 12 patients radiological examination revealed significant enlargement of the mediastinal lymph nodes. The hilar nodes were involved in all; the paratracheal nodes in nine. In general, the changes noted under therapy were less striking than those which occurred in the peripheral nodes. In no instance did the mediastinal lymph node enlargement entirely disappear. Ten of the patients, however, exhibited varying degrees of regression. In four the apparent shrinkage was striking. Only two patients have maintained the regression over the past year. All others relapsed usually to the degree seen prior to hormone administration.

Liver

Recent studies using the punch biopsy technique have demonstrated the frequency of hepatic involvement in sarcoidosis although the liver may not be enlarged (10). Occasionally disseminated lesions occur which are located principally in the periportal areas and a form of cirrhosis with ascites may result (11).

Hepatic enlargement was noted in nine patients in the present series. In addition to sarcoidosis one patient had chronic rheumatic heart disease with

evidence of congestive failure and is consequently excluded from this analysis. None of the patients had ever been jaundiced. Three of the nine complained of epigastric fulness after eating. One of these presented with the chief complaint of constant epigastric fulness, nausea, vomiting, and severe right upper quadrant pain and tenderness. In two cases mild right upper quadrant tenderness was noted. Laboratory evidence in three patients indicated moderately severe hepatic involvement with bromsulfalein retention of 1.9–2.0 mg/100 ml at 30 minutes, and in two of these the alkaline phosphatase activity was extremely elevated, 46.0 and 30.8 Bodansky units, without hypercalcemia or evidence of osseous involvement by x-ray. Four other patients had slightly elevated alkaline phosphatase activity (5–10 Bodansky units).

Of the patients exhibiting hepatomegaly the liver began to regress during treatment with ACTH as early as the second day and could no longer be palpated in six patients after 10 to 17 days. In the other two patients (Cases 12 and 13), those with the largest livers prior to treatment, there was an appreciable reduction in liver size but the organ remained palpable. The symptoms described above disappeared promptly. The patient with the most abdominal discomfort (Case 12) noted less epigastric fulness on the second day, no abdominal tenderness on the eighth day and no fulness after a hearty meal on the fourteenth day.

The changes in laboratory findings in the three patients with evidence of functional involvement are recorded in Table III. It is seen that in all the serum bilirubin concentration was within normal limits. By the end of the second week the BSP retention had been reduced from 1.9 and 2.0 mg.% to 0.6 and 0.4 mg.% respectively in the two patients in whom it was followed. There was a dramatic fall in the elevated alkaline phosphatase activity from 46.0 to 16.4 Bodansky units in one patient (Case 12) and from 30.8 to 7.3 units in the other (Case 13). Significant reductions were recorded by the end of the first week and were maximal at the end of the third week of treatment. Concomitant changes in the cephalin cholesterol flocculation and thymol turbidity were observed, but these may have been related to changes in the serum albumin and globulin concentrations which may or may not be associated with hepatic involvement in sarcoidosis. During the immediate post-treatment period there was a prompt, partial but striking recurrence of hepatomegaly and increased alkaline phosphatase activity, cephalin flocculation and thymol turbidity. Ten to 12 weeks after discontinuing ACTH the patients were asymptomatic and the liver was not palpable in any of the three. However, the laboratory findings remained moderately abnormal.

Spleen

Involvement of the spleen is frequently found in patients with generalized sarcoidosis and hematological abnormalities attributed to its involvement have been reported (1).

TABLE III

Functional Tests in Patients with Hepatomegaly

	PATIENT 12 (B. C.)				PATIENT 13 (I. H.)				PATIENT 1 (L. W.)			
	Before	During	2 wks. after	10 wks. after	Before	During	2 wks. after	10 wks. after	Before	During	2 wks. after	10 wks. after 3rd course
Hepatomegaly	5 cm.	1 cm.	3 cm.	0	5 cm.	2 cm.	2 cm.	0	3 cm.	0.5 cm.	3 cm.	0
Bilirubin (mg. per 100 ml.)	<0.8	<0.8			<0.8				1.1	1.2	<0.8	
Bromsulfalein retention (mg. per 100 ml. at 30 min.)	1.9	0.6			1.9	—			2.0	0.4	1.0	0.8
Alkaline phosphatase (units)	46.0	16.4	36.6	24.5	30.8	7.3	19.6	18.7	3.1	2.3	3.6	5.1
Ceph. flocc.	+++	+	0	+++	+++	0	++	+++	++	0	0	0
Thymol. turb. (units)	10.5	6.0	5.8	13.5	15.5	3.4	5.8	12.0	10.0	3.6	7.8	5.9
Serum albumin (gm. per 100 ml.)	3.6	4.9	4.2	3.9	4.6	4.9	4.3	4.3	3.6	4.3	3.7	4.4
Serum globulin (gm. per 100 ml.)	4.8	3.5	2.9	4.5	3.1	2.6	2.2	3.3	3.3	2.0	2.7	3.1

The spleen was readily palpable in nine of the 15 patients described in this report. The degree of enlargement varied between one and six cm. below the left costal margin. A decrease in size was noted as early as the second day of ACTH administration in some patients. In seven patients the spleen became impalpable during therapy. Generally, the larger spleens required longer periods of therapy for full regression. The patient with the largest spleen had a partial, but incomplete reduction in spleen size from six cm. to three cm. below the costal margin. No notes during the treatment period are available in the ninth patient (Case 15); however, at post-mortem examination two weeks after therapy the spleen was found to be three times normal size.

In three of the patients there was a partial return of splenic enlargement during the immediate post-treatment period, but at the most recent follow-up visit the spleen could not be palpated in any patient.

Uveo-Parotid Fever

The familiar picture of uveo-parotid fever characterized by a mild febrile reaction, uveitis, and swelling of the parotid glands often associated with facial palsy was described by Heerfordt (12).

Four of these patients demonstrated parotid gland involvement. In all, the glands were bilaterally enlarged, moderately firm and nodular. In each case there was a concomitant active uveitis and a low-grade fever. During ACTH administration this parotid enlargement disappeared in all instances. Appreciable diminution in gland size and nodularity was noted at some time between the seventh and the seventeenth day. After therapy there was a partial but transient recurrence in two patients at three weeks and three months respectively. In the other two patients the lesions have remained quiescent during a short observation period.

Hypercalcemia and Renal Disease

Hypercalcemia, which is not necessarily associated with bone changes on x-ray or with elevation of serum globulin, has been described frequently in patients with sarcoidosis (13). Hypercalcemia has been described in association with renal calculi and renal insufficiency (14).

Hypercalcemia was found in three patients of the present series prior to ACTH administration. In two patients the serum calcium concentration was greatly elevated—15.8 and 16.9 mg. per 100 cc. respectively. In the third patient the calcium elevation was less striking—12.5 mg. per 100 cc. Serum phosphorus and alkaline phosphatase activity were normal in all patients and the serum globulin concentration was elevated in only one of the three. Drs. John E. Howard and Theda R. Hopkins have performed studies on the calcium metabolism in these patients and through their courtesy the influence of ACTH and cortisone are reported here (Table IV). A fall in

TABLE IV

Effect of ACTH and Cortisone on Serum Calcium in Sarcoidosis

CASE	TREATMENT					SERUM CALCIUM CONCENTRATION (MG. PER 100 CC.)													FOLLOW-UP
							Day of treatment												
	Drug	Route	Initial dose mg.	Days	Total dose mg.	Before treatment	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
(3) J. C.	A	i.m.	100	7	550	15.8		12.9			10.9		9.8								11.3 at 1 week; 13.3 at 3 week
	C	i.m.	100	14	1400	13.8			13.4		13.4									10.9	Not significantly elevated during past 18 months
(5) J. E.	A	i.m.	100	11	700	16.9				13.2				11.2			10.7				
(15) R. N.	A	i.m.	100	9	720	12.5							11.2								9.0 at 3 days; died 1 week later

the serum calcium to within normal limits occurred in all four courses and with extraordinary rapidity, usually within one week at only moderate dosage levels.

All three patients had moderately severe renal disease with proteinuria, microscopic hematuria and casts, elevated non-protein nitrogen and severely impaired phenolsulfonphthalein excretion. It is of interest that these were the only patients in this series with appreciable renal difficulties. One case (Case 15) had shown rapidly progressing renal insufficiency in the hospital prior to treatment, the NPN rising from 59 to 134 mg. per 100 cc.; the PSP excretion being 17.5%. During ACTH the NPN continued to rise to 192 mg. per 100 cc. and then leveled off at 180 mg. per 100 cc. by the end of the course. The patient died at home ten days later. Microscopic sections of the kidneys reveal multiple cysts, areas in which the tubules are dilated, other areas in which atrophic tubules with flat epithelium are filled with eosin-staining material, and scars containing atrophic tubules and normal-appearing or hyalinized glomeruli. These lesions appear to be the results of obstruction of tubules and small vessels by the cysts. There is widespread focal calcification of tubules. There is no arterio- or arteriolar sclerosis. The glomeruli outside the focal scars appear normal. No sarcoid lesions are seen. The second patient (Case 5) had a blood NPN of 56 mg. per 100 cc. and a PSP excretion of 20%, neither of which changed during the short course of treatment. Vomiting which had been constant and severe during the ten days prior to ACTH disappeared after one day of treatment and has not recurred during the past 17 months. He has not returned for detailed studies.

The renal disease in the third patient (Case 3) was of the same severity as that of Case 5, NPN 58 mg. per 100 cc. and 20% PSP excretion. He has had four courses of hormonal therapy, three with ACTH and one with cortisone. The data on renal function, calcium and phosphorus blood levels and blood proteins over this two-year period are recorded in Table V. With the fall in the serum calcium during the first course (ACTH), temporary improvement in PSP excretion, nitrogen retention and findings on urinalysis occurred. During the second course (cortisone) when the serum calcium once again fell to normal, insufficient data are available to assess changes in renal function. Prior to the third course (ACTH) the serum calcium was normal. Nevertheless some improvement in renal function took place; the NPN decreased from 57 to 38 mg. per 100 cc., and PSP excretion increased from 29 to 39 per cent and the urea clearance rose from 34/40 to 78/52 per cent. The serum calcium and the NPN were both normal immediately before the fourth and last course (ACTH). Although the NPN rose slightly to 46 mg. per 100 cc. during treatment, the PSP and urea clearance both increased and the urinalysis findings remained unremarkable. Between January, 1950 and March, 1952 considerable improvement in renal function occurred. Perhaps these changes are the result

TABLE V

*Serial Laboratory Studies on Patient (3) (J. C. JHH 52403)**

DATE	SERUM CAL. MG. %	SERUM PHOS. MG. %	ALK. PHOS. UNITS	SERUM ALB. GM. %	SERUM GLOB. GM. %	NPN MG. %	P.S.P. % in 2 hrs.	UREA CL.	URINALYSIS			
									Sp. gr.	Alb.	RBC	Casts
1950—Jan.	14.5	5.1	3.7	4.0	2.7	57	20		1.011	++	±	++
Feb. before ACTH	15.8	5.9				58	16		1.008	++	0	+++
during ACTH	9.8	5.5		3.4	2.2	68	33		1.009	±	0	+
1 wk. after	11.3	3.7				41	20		1.008	0	0	++
Apr.	13.3	4.3				53			1.018	++	0	+++
Nov. before Cort.	13.8	3.6	4.4	4.2	3.1	60			1.012	±	++	+++
during Cort.	10.9	4.4							1.011	0	±	++
1951—May before ACTH	10.8	3.8		4.3	3.7	57	29	34/40	1.016	++	+	+++
during ACTH			5.4	4.3	2.0	38	39	78/52	1.014	0	0	+
1 wk. after	12.3	3.1		4.7	2.6	46						
1952—Mar. before ACTH	11.2	3.2	9.0	4.3	3.7	38	30	57/75	1.015	++	0	0
during ACTH	11.0	3.4	6.5	4.3	1.8	46	54	86/69	1.017	±	0	0

* See text.

of relief from hypercalcemia and nephro-calcinosis or, regression of sarcoid nodules within the kidney.

Muscles and Bones

Skeletal muscle lesions have been described in patients with sarcoidosis and Myers and his co-workers (15) have recently described several cases in which typical lesions were demonstrated by random muscle biopsy in the absence of any localizing signs or symptoms.

One of the patients in this series (Case 13) presented with severe generalized muscle wasting of at least two years duration. There was profound weakness in all of the skeletal muscles, but those about the pelvic girdle were most severely involved; the patient being unable to walk even with aid. The deep tendon reflexes had been difficult to obtain during the previous two years. A biopsy of the right rectus femoris revealed the muscle fibers to be atrophic and there was extensive seeding with epithelioid tubercles.

The patient was treated with ACTH over a period of four weeks and during this time there was gradual improvement. The patient was blind as a result of long-standing uveitis, but at the end of the period of treatment was able to walk with the aid of the nurse. The degree of improvement was confirmed by strength evaluations of the individual muscles performed by Miss M. E. Miller of the Physiotherapy Department. The improvement has been maintained during the three months since therapy was discontinued.

Radiological examinations of the hands and feet were carried out in all but one of the 15 patients. In three cases several phalanges revealed small areas of rarefaction. No changes in these lesions were seen when reexamined during ACTH or cortisone therapy in two cases. In the third case the radiological lesions in the toes were no longer present eight months after therapy. It is difficult to know whether or not this change can be ascribed to the administration of ACTH.

Miscellaneous Laboratory Findings

A mild anemia (hematocrit of less than 40%) was present in seven patients at the time of admission. It is difficult to assess the degree of hematopoiesis during ACTH or cortisone administration because of retention of fluid. However, two of the seven patients (Cases 4 and 13) had significant rises in the hematocrit values during treatment, from 32 to 42% and from 38 to 45% respectively. In four others no change in the hematocrit occurred whereas in one who received only a brief course of treatment the value fell from 39 to 34%. In only two patients were the elevations maintained after cessation of treatment.

Eosinophilia was not seen to any striking degree in this group of cases, only three having an absolute eosinophile count greater than 300 per cu. mm. The

eosinopenic response to hormone therapy was satisfactory in all but two instances; in one (Case 3) during a brief period on small doses of cortisone, and in the other (Case 14) in association with a hypersensitivity reaction to ACTH.

In 11 patients the erythrocyte sedimentation rate was greater than 25 mm. per hour. During treatment it fell significantly in all instances and in eight cases to within normal limits (less than 10). In three patients who maintained remissions of appreciable duration after termination of therapy the sedimentation rate remained normal.

Twelve of the 15 patients had serum globulin values greater than 3.0 gm.%, in eight cases the level being 3.6. During therapy the average drop in these values was 1.5 gm.%; the range between 0.4 and 2.9 gm.%.

The cephalin-cholesterol flocculation test was positive in nine of the 12 patients in whom it was determined. In six it became negative during treatment. There were similar changes in the thymol turbidity reaction. Of seven patients with values greater than 5.0 units on admission, five demonstrated a fall to within normal limits (less than 5.0) during treatment and in two patients there was a fall from 12.8 to 5.8 and from 10.5 to 6.0 units respectively. In one patient (I. W.) following treatment both the cephalin flocculation and the thymol turbidity reactions relapsed promptly to the high pre-treatment values. This patient had severe hepatic involvement, presumably on the basis of sarcoidosis. In two other patients with less severe liver involvement these determinations also increased slightly after treatment. However, in the remainder both tests revealed normal values during the follow-up period.

In five of the patients the tuberculin tests have been repeated during the period after treatment, but no significant increases in sensitivity were demonstrated.

Discussion

There can be no question that a profound and striking improvement in sarcoidosis can be effected during the administration of either ACTH or cortisone. This has been reflected in symptomatic relief and in numerous objective observations both clinical and functional. Lesions may heal and show no trace of their presence, but when relapse occurs those in the skin have tended to reappear in the same location. The rapidity and degree of tissue change in sarcoid lesions brought about by a heightened level of adrenocortical activity might be considered as evidence against the theory that this disease might be a form of tuberculosis. Further study of the course of the tissue change by serial biopsy might throw further light on the specific nature of the process. From the meager evidence thus far accumulated it would appear that if intensive treatment is given the lesions heal with little or no scarring.

Early in this study only moderate doses of ACTH and cortisone were

utilized. As a result the improvement was sometimes very slow and equivocal. Later with ACTH given intravenously the beneficial results were beyond question and it would appear that intensive treatment should be given at the start to insure maximal improvement. In this series of cases treatment has been restricted largely to those cases showing functional impairment of a serious degree in an important structure such as severe uveitis or extensive pulmonary infiltration. This was done not only to make the evaluation of the effectiveness of treatment on the lesions of sarcoidosis more reliable, but also because of the possible danger of the development of tuberculosis. Thus far, this latter possibility has not materialized.

In the present cases there has been a mixed pattern as to the course of the disease after cessation of treatment. In some a prolonged remission has been achieved, in others a prompt relapse has occurred, and in still others continued quiescence of some lesions and reactivation of others. If one is dealing with very serious functional difficulty which may become permanent with long continued activity it may be advisable to give continuous therapy over longer periods of time than in most of the present cases. The data presented here on the course after treatment is still insufficient to tell whether these hormones may significantly alter the overall course of sarcoidosis. The results to date probably indicate a suppression of activity during treatment and when treatment is ended the occurrence of relapse will depend on the natural course of the disease in the given patient rather than on one or more variables associated with the treatment.

Improvement seems to occur in all areas in which the sarcoid lesions are present, provided they are active. Scarring and reduction of function from old inactive lesions is not influenced in a favorable fashion. The uveal tract seems to be a fairly sensitive indication and relapse may be detected earlier in this area than, for instance, in the pulmonary system. When reactivation of uveitis alone is the pattern of the relapse and if it is in the anterior segment of the eye, it would seem reasonable to utilize cortisone ophthalmic ointment and withhold systemic administration of either hormone if this is successful.

The data are too meager for comparison of the relative effects of ACTH and cortisone. There seems no doubt that both can produce a remission during their continued administration. The effects under cortisone have been a little slower in their appearance and in their degree but this is probably because less intensive treatment was given than with ACTH.

Just as is the case in the treatment of patients with active disseminated lupus erythematosus (16) several of these patients had a transient relapse with cessation of treatment which has been designated as the "rebound" phenomenon. This was characterized by some elevation of temperature and reappearance of a variety of other aspects of the disease such as uveitis, depression of pulmonary function, and further enlargement of lymph-nodes,

liver and spleen. In some cases these manifestations would spontaneously regress in from one to four weeks. It would seem reasonable, certainly after the first course of treatment, to wait for this period of time if possible before reinstituting therapy should a relapse occur.

One other point has been of interest clinically. Many times there has been a discrepancy between the symptomatic improvement and the objective evidence of change in the involved area. For instance, there may be great improvement in the degree of dyspnea and yet no concrete change can be seen in the roentgenogram of the chest. Also when there has been extensive clearing of the pulmonary infiltration and disappearance of dyspnea during treatment, the radiological findings may reappear to a large degree after cessation of treatment with no evident reduction in the degree of symptomatic improvement. It has been noted in the natural courses of the disease that the degree of symptomatic difficulty cannot be predicted from the appearance of the pulmonary lesion by x-ray.

SUMMARY

1. Fifteen patients exhibiting a broad variety of the manifestations of active sarcoidosis have been treated with one or more courses of adrenocorticotropic hormone (ACTH) or cortisone.

2. Under heightened adrenocortical activity a striking regression of the signs and symptoms of active disease occurred almost universally.

3. The organ systems, in which long-continued activity of sarcoid had produced extensive fibrotic change, demonstrated little, if any, improvement.

4. The pattern of events after cessation of treatment has varied considerably. In some patients a prolonged remission has been obtained, in others a prompt relapse has occurred, and in the remainder continued suppression of some manifestations and reactivation of others have occurred. A few patients have, after a prompt relapse, once again entered into a period of remission.

5. Eight of eleven patients with a history of appreciable weight loss before treatment, gained weight during and after treatment. Fever and tachycardia were reduced during treatment in all patients.

6. Dramatic inactivation of the lesions of acute sarcoid uveitis was observed in eight patients. Return of vision, however, occurred only in those patients in whom the onset of severe uveitis was recent. The tendency towards relapse was great. The topical application of cortisone ophthalmic ointment suppressed the signs of active anterior uveitis in two patients. Other ocular manifestations such as retinitis and conjunctival nodules, were similarly suppressed.

7. Respiratory symptoms, even of great severity, entirely disappeared during ACTH or cortisone treatment; after discontinuing treatment most of the patients remained symptom-free. Pulmonary signs also cleared during treat-

ment and remained so after treatment, save for a transient recurrence immediately after treatment in half the patients. Striking changes were seen also on the x-ray examination. Although the lesions on x-ray did not clear completely, they did change in four patients to a degree such that they were not recognizable as sarcoid. After analysis of the detailed pulmonary function studies which were performed in seven patients, it appeared that the changes in the vital capacity correlated better with the changes in the patients' symptoms, signs and x-ray findings than did the changes in any of the other functional determinations.

8. The various skin and subcutaneous manifestations entirely cleared in nine of ten patients. In five, the lesions gradually reappeared after one to nine months; in the remaining four, the lesions have not reappeared.

9. Enlarged peripheral lymph nodes were no longer felt in eleven of thirteen patients during hormonal treatment and remained impalpable during the post-treatment period in six. Regression of the enlarged mediastinal lymph nodes during treatment was observed in ten of twelve patients, but the regression was in no instance complete and after treatment, relapse, usually to the degree seen before treatment, occurred in eight.

10. Full regression of hepatic and splenic enlargement occurred in the majority of patients. There were also striking reductions in the elevated bromsulphalein retention in two patients and in the grossly elevated alkaline phosphatase activity also seen in two patients. Evidence of liver disease returned in most patients, but in no instance to the degree seen prior to treatment.

11. Of the four patients with "uveo-parotid fever", the enlarged, nodular parotid glands regressed in all to normal size during treatment. In two, after therapy, there was a partial, but transient, recurrence; in the other two, no recurrence.

12. The serum calcium concentrations decreased rapidly to within the normal range in three patients exhibiting hypercalcemia. In all three, moderately severe renal disease was also present. In one patient studied over a two-year period, during which four courses of ACTH or cortisone were given, renal function improved.

13. Increased muscle strength was noted both during and after ACTH in a patient with severe muscular wasting due to extensive seeding of the muscles with sarcoid tubercles.

14. No significant change occurred during treatment in the three patients demonstrating rarefaction of bone by x-ray prior to treatment.

15. In most patients during hormone administration there were striking reductions in the erythrocyte sedimentation rate, serum globulin concentration, cephalin-cholesterol flocculation and thymol turbidity. Anemia disappeared in two patients.

16. To date none of the patients has exhibited clinical evidence of tuberculosis during or after treatment; nor did an increase in tuberculin sensitivity develop in the five patients in whom it was determined before and after treatment.

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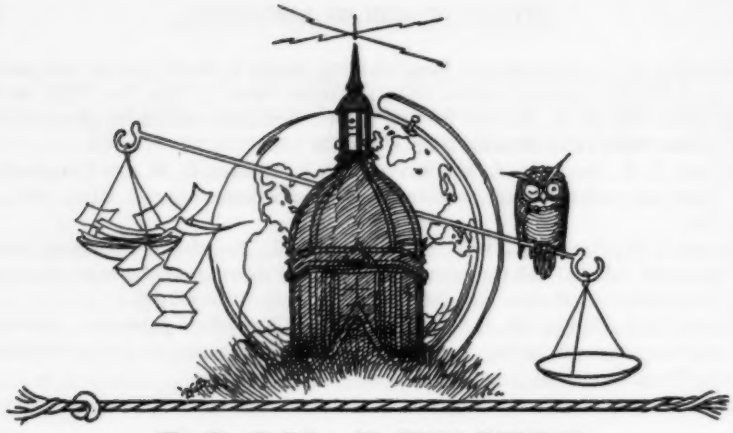

BOOK REVIEW

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of the Bulletin)

Surgical Forum Clinical Congress of the American College of Surgeons, 1951. 667 pp., $10.00. *W. B. Saunders Co., Philadelphia, Pa.*

This is the second of a proposed series of volumes recording reports given at the Surgical Forum on Fundamental Surgical Problems of the American College of Surgeons. This volume of the 1951 session contains 117 papers by 341 contributors to a wide variety of fields of current surgical research. Articles are brief (limited to 3000 words) but of length adequate for all except those seriously interested in a particular problem. Such a style of reporting and publishing allows workers to publish fairly complete early reports of their work and readers to learn readily of current work in various fields. It has much to recommend itself for wider use. Papers are grouped under various specialties and biological systems covering all fields of surgical research so that one may easily select a particular section of interest to him. The volume will be of interest to those who wish to browse over short, interesting scientific papers and invaluable for those who wish to come abreast of current surgical research.

HENRY T. BAHNSON

Culdoscopy. A New Technic in Gynecologic and Obstetric Diagnosis. By ALBERT DECKER. 148 pp., $3.50. *W. B. Saunders Co., Philadelphia, Pa.*

"Culdoscopy," a monograph by Albert Decker, Clinical Professor of Gynecology and Obstetrics at New York Polyclinic Medical School and Hospital, producer and developer of the culdoscope, is the fifth of The American Monograph Series published by W. B. Saunders Company, 1952. The foreword is written by Richard W. TeLinde, Professor of Gynecology, and head of The Department of Gynecology at Johns Hopkins Hospital, who has had wide experience with the culdoscope.

The thirteen chapters of the monograph discuss in logical sequence the history of abdominal endoscopy with the development of the culdoscope, the anatomy of the vagina as related to the procedure, and the technique of, and indications for, culdoscopy. The details of the instrument and procedure are covered minutely so that these chapters could serve as a manual for the neophyte. Excellent photographs and illustrations, many of the latter by William Didusch, enhance the value of this work.

Chapters dealing with ectopic pregnancy and sterility cover in great detail the comparative value of various diagnostic aids with special reference to culdoscopy, and needling of the cul-de-sac and pneumoperitoneum as a diagnostic procedure is adequately discussed. The volume closes with several typical case reports of successful uses of the instrument. Although the author uses either local or regional, and is opposed to general anesthesia, we have used the latter almost exclusively without ill effects. The very rare, but startling, complication of puncture of a viscus is not mentioned. Fortunately our only case of such complication had an uneventful convalescence, but such might not always be the case.

This volume is recommended as presenting a beautifully detailed description of the technique of culdoscopy with an equally detailed if somewhat optimistic picture of the value of the instrument.

J. DONALD WOODRUFF

BOOKS RECEIVED FOR REVIEW

Basic Medical Physiology. By W. B. YOUMANS. 436 pp., $7.50. *Year Book Publishers, Inc., Chicago, Illinois.*

Carbohydrate Metabolism. Correlation of Physiological, Biochemical and Clinical Aspects. By S. SOSKIN and R. LEVINE. 346 pp., $8.50. *University of Chicago Press, Chicago, Illinois.*

Diseases of the Nervous System in Infancy, Childhood and Adolescence, 3rd edition. By FRANK R. FORD. 1181 pp., $18.50. *Charles C Thomas, Springfield, Illinois.*

Pharmacology in Clinical Practice. By HARRY BECKMAN. 839 pp., $12.50. *W. B. Saunders Co., Philadelphia, Pa.*

Textbook of General Surgery, 6th edition. By W. H. COLE and R. ELMAN. 1154 pp., $12.50. *Appleton-Century-Crofts, Inc., New York.*

Textbook of Gynecology, 4th edition. By EMIL NOVAK and EDMUND R. NOVAK. 800 pp., $9.00. *Williams & Wilkins Co., Baltimore, Md.*